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Original Communications

THE EFFECT OF ORAL FEEDING AT DIFFERENT LEVELS ON THE ABSORPTION OF FOODSTUFFS IN INFANTILE DIARRHEA

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THE incidence of infantile diarrhea has greatly decreased in this country during the past half century, and advances in therapy, particularly in regard to the administration of parenteral fluids and parenteral alimentation, have greatly reduced the mortality rate. Nevertheless diarrheal disease continues in our midst, showing periodic outbreaks, and even under the best of conditions fatalities have not been eliminated. It has been our impression that nutritive failure was responsible for most of the fatalities. Since the best parenteral nutrition is not ideal, it occurred to us that oral nutrition was perhaps not being used to the greatest advantage and that the possibility of using it to better advantage deserved careful study. It seemed desirable in particular to investigate the current practice of early therapeutic starvation.

The policy of sharply reducing the oral intake or eliminating oral food entirely at the onset of the attack with a very cautious and gradual increase after a period of days has been the generally accepted procedure both in this country and abroad. When an increasing oral intake was followed by an exacerbation of the diarrhea it was generally assumed that the food was increased too rapidly, and a second period of therapeutic starvation was tried and sometimes even a third. This regimen is based on theoretical concepts that have never been critically tested. Our predecessors placed their reliance on the appearance and number of stools as the criterion of success of treatment, and since withholding food reduced the volume and frequency of the stools it was assumed that this was beneficial. This point of view was sharply challenged in 1924 by Park,¹ who maintained that the child rather than the stools should be taken as the criterion for evaluating therapy. Although his point of view has been influential in pediatric thinking, the fact remains that changes in the stools are more readily assessed than changes in the clinical state of the patient; the possible benefit

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from increased feeding is not insufficiently apparent to outweigh the emotions engendered in the spectators by an increased number of stools, and the stools still tend to dominate therapy.

A second theoretical consideration that has favored therapeutic starvation is the belief that food will stimulate digestive secretions and in the presence of severe peristalsis these secretions will be carried out, resulting in a net loss of electrolytes to the body. Whether or not such a net loss is induced by food in severe diarrhea is not actually known. Finally there is a belief that the withdrawal of food is beneficial by resting the intestine, which is thought to hasten recovery. This again has never been convincingly demonstrated.

It appeared to us that the value of therapeutic starvation could be accurately assessed by two studies: (1) a metabolic study of the assimilation of the various nutrients at different levels of feeding, which would show whether the restriction of food favors or decreases assimilation; and (2) a statistical study of patients treated alternately by therapeutic starvation and by full feeding, in which the clinical course of the illness was compared. The present communication deals with such a metabolic study. A succeeding report² describes such a clinical study.

EXPERIMENTAL

Subjects.—The subjects employed for this study were male infants who were admitted to the Children's Medical Service of Bellevue Hospital for the treatment of diarrhea or who developed the disease on the ward. They varied from 12 days to 3 months in age and weighed from 2.5 to 5.3 kilograms. Enteric pathogens were not cultivated from the stools in any instance, and although attempts to establish a virus etiology were not made, it was believed that parenteral infection was responsible for the diarrhea in these patients. Initially all presented a picture of dehydration, acidosis, and toxicity of varying degree, which required restorative measures with parenteral fluids. Immediately after parenteral fluid administration the infants were transferred to the metabolism ward, where they were placed on frames for the separate collection of urine and feces.

Metabolism Periods.—An inherent difficulty in making comparisons of different diets is the possibility that the severity of the diarrhea may be altered during the period of study by factors quite apart from the food. It is obviously impossible to compare two successive experimental diets when the diarrhea is spontaneously waxing or waning; the diarrhea should be of comparable severity at the start and at the close of the observations. Since most of the diarrheas were of relatively short duration this necessitated short metabolism periods. We found it necessary to employ metabolism periods of only twenty-four hours' duration in order to make two or three observations on each subject before the picture had changed, and a number of subjects upon whom work had been started had to be eliminated because of obvious change in the status of the disease before a second period could be completed. Data were eventually obtained on six infants in whom the severity of the process was comparable. A metabolism period as short as twenty-four hours would not be suitable for most purposes because of irregularity and possible delay in intestinal evacuations; in the case of severe diarrhea, however, short periods do not involve this difficulty.

The feedings given during each period consisted of evaporated milk, corn syrup, and water, in proportions and concentrations comparable to those in daily use on the wards. This was done deliberately because it was thought advisable to judge the efficacy of a food which is commonly employed and of proved digestibility rather than to use a formula altered in composition and proportions on which claims for superior absorption might be made on the basis of our study. Infants were given a low calorie formula (30 to 45 calories per kilogram of body weight) or were completely starved, followed by a medium (60 to 69 calories per kilogram) or a full calorie formula (100 to 137 calories per kilogram). In some instances the higher feeding was given first. Apart from the measured amount of evaporated milk formula, the infants were offered water freely, but if clinical evidence of water deficit was present it was made up by parenteral 5 per cent dextrose in water. The beginning and end of each test period was identified in the stool by charcoal or carmine, which had been added earlier to the formula. At the end of the study period the infants were given parenteral fluids if needed and maintained on full calorie feedings until complete recovery took place as evidenced by complete cessation of diarrheal stools and progressive gain in weight for at least one week.

Analysis of Food and Excreta.—Aliquots of food, urine, and dried feces were analyzed for ash, sodium, potassium, chloride, calcium, fat, and nitrogen. The analytical procedures employed are listed.³⁻⁸

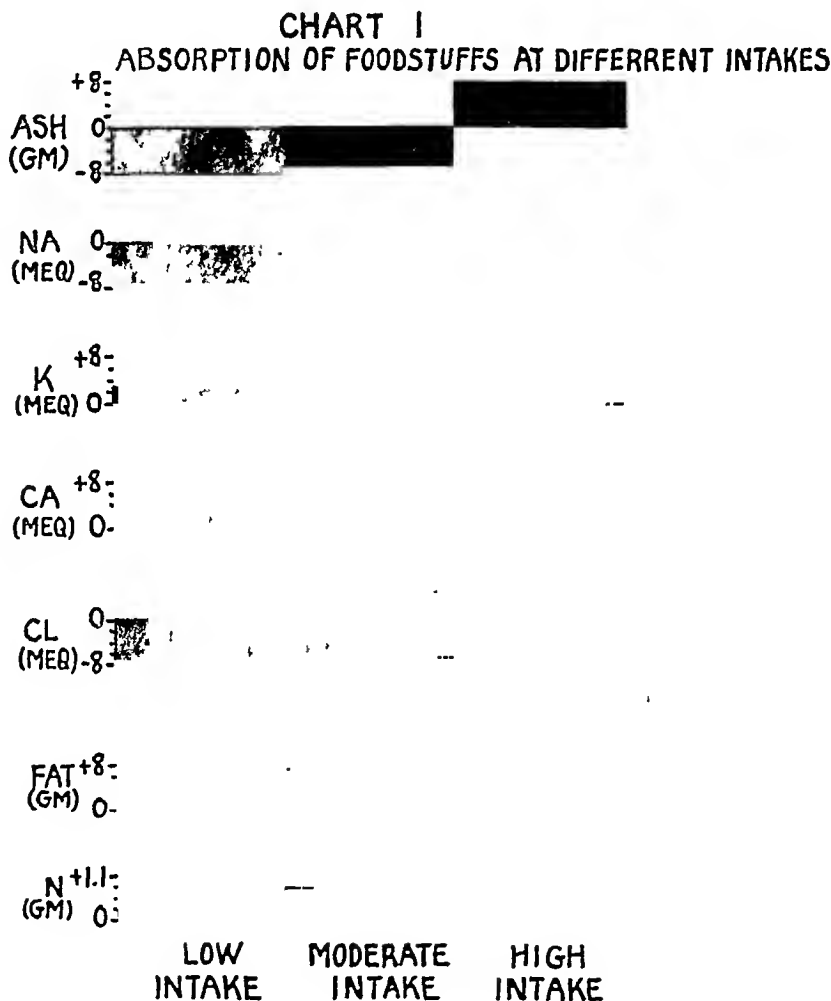
RESULTS

Of a total of twenty-one patients with infantile diarrhea transferred to the metabolism ward for study, complete metabolic data were obtained on six. Brief protocols of these six with tabulated results and absorption charts are presented.

CASE 12.—R. H. was a 10-week-old white male infant admitted June 6, 1946, because of acute bronchitis. One week later he developed an otitis media and a mild diarrhea which became progressively worse. Treatment had consisted of parenteral physiologic saline and reduced oral food. He was transferred to the metabolism ward three days after the onset of diarrhea and appeared alert, hungry, and fairly well hydrated although he was having twelve watery movements a day. He was offered a formula of 30 calories per kilogram of body weight for the first twenty-four-hour period. The next day he had lost 200 Gm. and looked moderately dehydrated and less active. The second and third test periods provided 60 and 100 calories per kilogram for the intake respectively. A weight loss of 150 Gm. was sustained between these two periods; however, there was no further weight loss while he was maintained on 110 calories per kilogram, and ten days later the diarrhea subsided completely and he began to gain weight progressively. The only parenteral fluids necessary while under our observation were 320 c.c. of equal parts of normal saline and 5 per cent dextrose, given immediately after the metabolic observations were completed. A summary of the data is shown in Table I. Absorption values for all the food constituents investigated are shown in Chart 1.

CASE 26.—R. P. was a 12-day-old white male infant who developed a gradually progressive diarrhea on the third day of life. He was a small, poorly

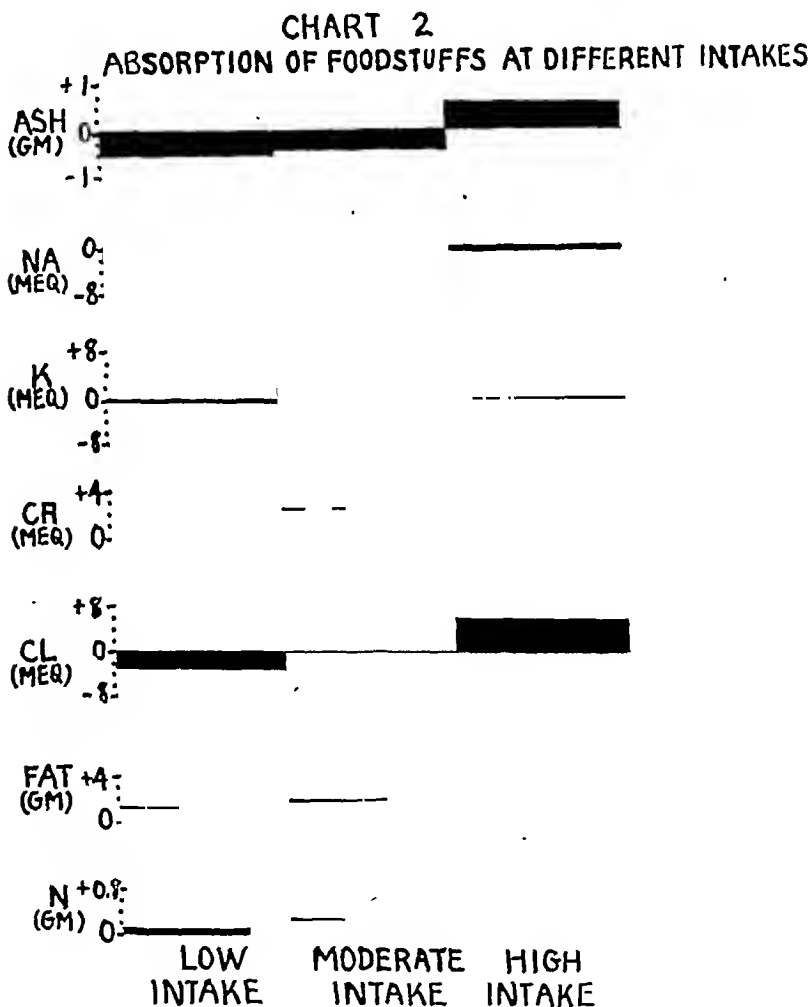
nourished, moderately dehydrated infant, who had small green watery evacuations numbering seventeen to twenty per day. Initial hydration with parenteral saline and sodium lactate solutions was followed by three test periods on the metabolism frame, the data from which are shown in Table II and Chart 2. The infant was unable to maintain himself in water balance by oral fluids alone, and



5 per cent dextrose in water had to be given parenterally during each of the three test periods. He was maintained on 120 calories per kilogram by mouth with parenteral fluid supplements when necessary. On the ninth day after admission the diarrhea subsided, and he thereafter gained steadily in weight.

CASE 22.—L. II. was a 6-week-old white male infant admitted Nov. 9, 1946, with a two-week history of cough, cold, and diarrhea, the latter becoming increasingly worse. He had a purulent discharge from the right drum on admission. Group A hemolytic streptococcus was isolated from the discharges of the

nose, throat, and right ear, and on one occasion from the blood stream. Prior to transfer to the metabolism ward he had received lactate Ringer's solution parenterally and a reduced feeding orally. Data on two test periods with intakes of 45 calories per kilogram and 100 calories per kilogram were obtained as shown in Table III and Chart 3. At the end of the first period the infant looked moderately dehydrated, which finding was supported by marked oliguria and



a weight loss of 195 Gm. During the next period, water was forced between feedings and the baby was very closely watched. Although the urinary flow improved somewhat he appeared apathetic and was markedly dehydrated, so it was decided to introduce fluids parenterally. Because of an error, 100 c.c. of normal saline instead of 5 per cent dextrose was given. After the end of the second test period the baby received vigorous parenteral fluid therapy and was maintained on 110 calories per kilogram of oral food. Four days later his diarrhea subsided completely, and he was showing daily gains in weight.

TABLE I. CASE 12

	WATER (C.C./DAY)	ASH (GM./DAY)	Na. (MEQ./DAY)	K. (MEQ./DAY)	Cl. (MEQ./DAY)	Cl. (MEQ./DAY)	FAT (GM./DAY)	N. (GM./DAY)	WT. (KG.)
Oral intake	735	1.20	4.0	5.9	9.8	4.4	5.90	0.82	5.34
Urine	370	*	0.1	13.8	2.4	12.1	0.74	0.74	
Feces	208	2.02	19.3	3.0	3.2	19.8	1.65	0.49	
Absorbed	+572	-0.92	-15.3	+2.9	+6.6	-15.4	+4.25	-0.33	
% Intake absorbed	+72	-68	-380	+50	+68	-349	+72	+40	5.14
Oral intake	1005	2.40	8.0	11.8	19.6	8.8	11.80	1.64	
Urine	175	*	0.1	11.9	1.6	1.4	0.69	0.69	
Feces	267	3.08	13.0	5.4	13.0	22.2	3.86	0.82	
Absorbed	+738	-0.68	-5.0	+6.4	+6.6	-13.4	+7.91	+0.82	4.99
% Intake absorbed	+74	-22	-62	+55	+34	-150	+67	+50	
Oral intake	840	3.84	12.7	18.9	30.0	14.2	18.90	2.62	
Urine	87	*	0.1	14.0	0.9	0.8	0.79	0.79	
Feces	275	3.21	16.8	8.0	15.0	16.9	7.60	0.96	4.99
Absorbed	+565	+0.59	-4.1	+10.9	+15.0	-2.7	+11.30	+1.66	
% Intake absorbed	+67	+16	-32	+59	+50	-19	+60	+63	

*Ash in urine not determined.

TABLE II. CASE 26

	WATER (C.C./DAY)	ASH (GM./DAY)	Na. (MEQ./DAY)	K. (MEQ./DAY)	Cl. (MEQ./DAY)	Cl. (MEQ./DAY)	FAT (GM./DAY)	N. (GM./DAY)	WT. (KG.)
Total intake	560*	0.56	2.0	3.0	4.6	2.4	2.62	0.41	2.59
Urine	190	0.16	0.3	14.0	0.3	4.5	0.24	0.24	
Feces	111	1.09	10.3	3.6	4.2	5.7	1.36	0.30	
Absorbed	+449	-0.53	-8.3	+0.4	+0.6	-3.3	+1.26	+0.11	
% Intake absorbed	+80	-95	-120	-22	+9	-135	+48	+27	2.52
Total intake	1210†	1.12	4.0	6.0	9.2	4.8	5.24	0.82	
Urine	430	0.19	0.3	13.5	0.2	5.7	0.23	0.23	
Feces	202	1.60	8.2	4.1	6.7	4.8	3.20	0.49	
Absorbed	+1008	-0.48	-4.2	+1.9	+2.5	0	+2.04	+0.33	2.55
% Intake absorbed	+83	-43	-104	+30	+27	0	+39	+40	
Total intake	810‡	2.24	8.0	12.0	18.4	9.6	10.48	1.64	
Urine	355	0.53	0.5	19.5	1.5	15.4	0.35	0.35	
Feces	151	1.64	8.9	3.9	14.9	3.3	4.30	0.43	2.57
Absorbed	+659	+0.60	-0.9	+8.1	+3.5	+6.3	+6.18	+1.21	
% Intake absorbed	+81	+27	-11	+62	+19	+53	+59	+74	

*Represents addition of 100 c.c. of 5 per cent dextrose parenterally to oral intake.

†Represents addition of 670 c.c. of 5 per cent dextrose parenterally to oral intake.

‡Represents addition of 380 c.c. of 5 per cent dextrose parenterally to oral intake.

TABLE III. CASE 22

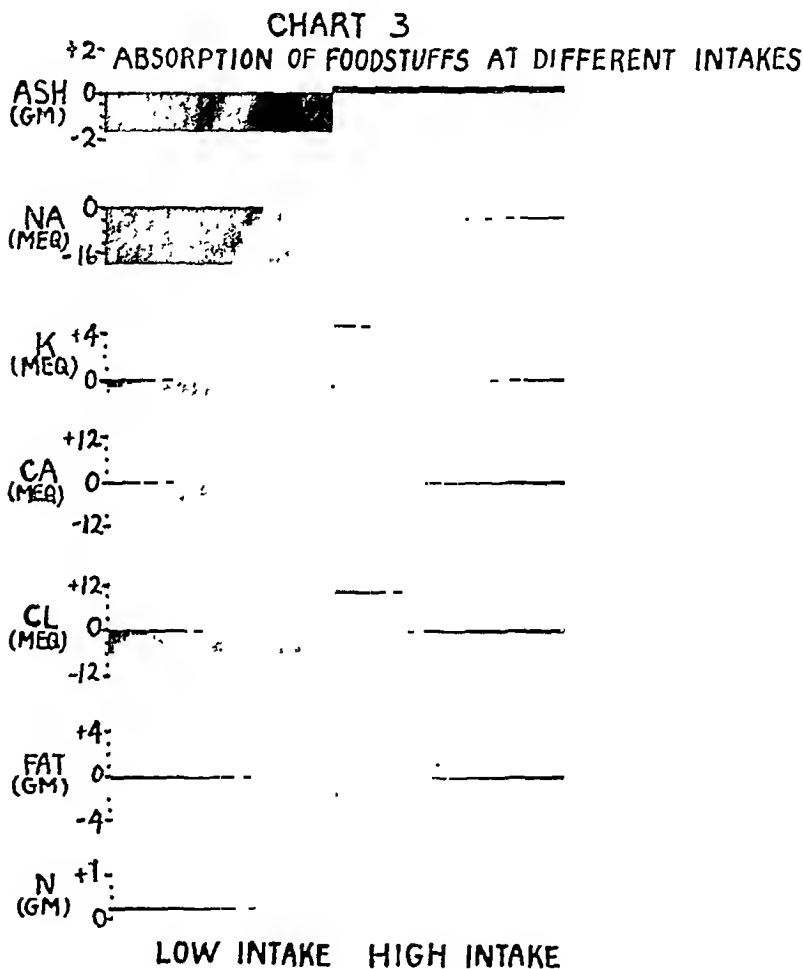
	WATER (C.C./DAY)	ASH (GM./DAY)	Na. (MEQ./DAY)	K. (MEQ./DAY)	Ca. (MEQ./DAY)	Cl. (MEQ./DAY)	FAT (GM./DAY)	N. (GM./DAY)	WT. (KG.)
Oral intake	195	0.96	3.3	4.8	7.4	3.9	4.73	0.66	3.84
Urine	20	0.12	0.4	4.7	0.1	5.5		0.11	
Feces	285	2.62	22.9	6.2	13.6	10.0	6.00	0.41	
Absorbed	-90	-1.66	-19.7	-1.4	-6.2	-6.1	-1.27	+0.25	
% Intake absorbed	-46	-173	-620	-31	-87	-137	-27	+38	3.78
Total intake	810*	3.77*	24.0*	14.4	22.4	26.2*	14.20	1.97	
Urine	58	0.49	1.3	3.1	0.7	10.9		0.53	
Feces	460	3.51	28.0	9.6	19.2	15.5	10.00	0.67	
Absorbed	+350	+0.26	-4.0	+1.8	+3.2	+10.7	+1.20	+1.30	3.58
% Intake absorbed	+50	+7	-16	+33	+15	+41	+30	+66	

*Represents addition of 100 c.c. of normal saline parenterally to oral intake.

TABLE IV. CASE 23

	WATER (C.C./DAY)	ASH (GM./DAY)	Na. (MEQ./DAY)	K. (MEQ./DAY)	Ca. (MEQ./DAY)	Cl. (MEQ./DAY)	FAT (GM./DAY)	N. (GM./DAY)	WT. (KG.)
Oral intake	645	4.32	14.3	21.3	33.7	15.9	21.30	2.96	3.60
Urine	86	1.10	0.6	24.8	0.3	4.5		1.08	
Feces	230	3.03	13.4	8.6	31.0	12.2	10.90	1.19	
Absorbed	+115	+1.29	+0.9	+12.7	+2.7	+3.7	+10.40	+1.78	
% Intake absorbed	+64	+30	+6	+60	+8	+24	+49	+60	3.54
Oral intake	585	2.16	7.2	10.7	16.9	7.9	10.65	1.48	
Urine	140	0.76	0.4	32.2	0.1	3.4		0.45	
Feces	233	1.82	8.7	6.0	14.4	10.7	3.18	0.55	
Absorbed	+352	+0.34	-1.5	+4.7	+2.5	-2.8	+7.47	+0.93	3.44
% Intake absorbed	+60	+16	-21	+44	+15	-35	+70	+63	

CASE 23.—D. T. was a 2-month-old white male who developed a mild diarrhea on the ward; this subsided only to return with marked severity, whereupon he was transferred to the metabolism ward. In order to answer the criticism that the diarrhea may have become less severe by the time the last period of full feedings was reached, the usual feeding procedure was reversed. For the first



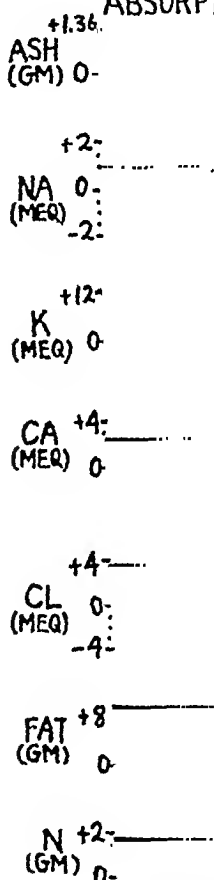
twenty-four hours a full caloric diet was given, while half the number of calories were offered for the second period. The data on Table IV and Chart 4 show that the higher intake caused better absorption regardless of the time offered. Five days after completion of the tests, while he was on 100 calories per kilogram his diarrhea stopped abruptly. At no time while under our observation were parenteral fluids needed.

CASE 27.—A. G. was a 7-week-old Puerto Rican boy who was admitted Jan. 19, 1947, as a boarder. Ten days later he developed capillary bronchitis and bilateral otitis media followed by severe diarrhea. He was treated with parenteral

electrolytes, dextrose, and whole blood, and complete oral starvation was instituted nineteen hours before transfer to the metabolism ward. He was still having as many as twenty watery stools daily at this time. It was decided to give the infant one period of full feeding followed by one of complete starvation (Table V). Supplementary 5 per cent dextrose solution was administered during both periods. The infant took a full diet well and had dextrose and normal saline as needed parenterally. Six days after his last test period the diarrhea ceased and recovery was uneventful.

CHART 4

ABSORPTION OF FOODSTUFFS AT DIFFERENT INTAKES



HIGH INTAKE MODERATE INTAKE

CASE 28.—J. R. was a one-month-old white male infant who had received an exsanguination transfusion at birth because of erythroblastosis fetalis. He was doing well when he developed diarrhea on the ward. As in the previous patient, periods on full feedings and complete oral starvation were studied (Table VI). The fluid intake was augmented in each period by 150 c. c. of 5 per cent

TABLE V. CASE 27

	WATER (C.C./DAY)	ASH (GM./DAY)	Na. (MG./DAY)	K. (MG./DAY)	Ca. (MG./DAY)	Cl. (MG./DAY)	PAT (GM./DAY)	N. (GM./DAY)	WT. (KG.)
Total intake	835*	3.81	12.7	18.9	30.0	11.2	18.90	2.62	1.14
Urine	20	0.05	0.01	5.0	0.1	2.2		0.11	
Feces	361	3.06	18.5	7.2	18.0	11.9	6.03	0.65	
Absorbed (106 cal./kg.)	+171	+0.78	-5.8	+11.7	+12.0	-0.7	+12.87	+1.97	
% Intake absorbed	+57	+20	-46	+62	+10	-5	+68	+75	
Total intake	1055†	0	0	0	0	0	0	0	3.96
Urine	700	0.39	1.3	61.0	0.7	11.0		0.79	
Feces	178	1.43	6.7	5.7	5.8	8.2	2.22	0.30	
Absorbed	+877	-1.43	-6.7	-5.7	-5.8	-8.2	-2.22	-0.30	

*Represents addition of 250 c.c. of 5 per cent dextrose parenterally to oral intake.

†Represents addition of 950 c.c. of 5 per cent dextrose parenterally to oral intake.

TABLE VI. CASE 28

	WATER (C.C./DAY)	ASH (GM./DAY)	Na. (MG./DAY)	K. (MG./DAY)	Ca. (MG./DAY)	Cl. (MG./DAY)	PAT (GM./DAY)	N. (GM./DAY)	WT. (KG.)
Total intake	847*	2.89	9.4	14.4	22.5	10.7	14.20	1.98	2.79
Urine	370	1.55	15.4	17.0	1.2	24.4		0.76	
Feces	176	3.26	7.5	6.1	21.7	7.8	7.66	0.69	
Absorbed (100 cal./kg.)	+671	-0.37	+1.9	+8.3	-2.2	+2.9	+6.51	+1.29	
% Intake absorbed	+79	-13	+20	+57	-10	+27	+16	+65	
Total intake	653*	0	0	0	0	0	0	0	2.67
Urine	460	0.34	1.2	10.2	0.5	5.3		0.57	
Feces	67	0.59	7.0	3.3	19.2	5.1	0.51	0.15	
Absorbed	+586	-0.59	-7.0	-3.3	-19.2	-5.1	-0.51	-0.15	

*Represents addition of 150 c.c. of parenteral 5 per cent dextrose in water to oral intake.

dextrose parenterally. The diarrhea improved slowly one week after he was placed on a 110 calories per kilogram diet, and he was discharged with occasional loose stools but with a consistent weight gain.

COMMENT

The results are entirely consistent in the six cases presented in that increased absorption of all the food elements studied resulted from the higher food intake. A breakdown of the data into its individual food components follows.

Water: The volume of stool water serves as an index of the severity of the diarrheal process. Volumes over 200 c.c. per day, which were excreted by most of our patients, are indicative of severe diarrhea.⁹ The smaller volumes observed in Case 26 are still significant as the infant weighed considerably less than the others in the series.

The conservation of water by the kidneys to compensate for the large fluid loss in the stools is demonstrated in almost all patients, but particularly in Cases 22 and 27, where a striking oliguria of 20 c.c. of urine per day was observed.

No effort was made to force water between feedings as it was important for our study that the measured amount of formula was taken without refusal or vomiting. Water deficits when present were made up by parenteral dextrose solution without electrolytes to prevent the complicating factor of parenteral absorption of minerals with subsequent excretion into the gut, which would invalidate the data on intestinal absorption. If it were not for the necessity of controlling conditions for the study it would certainly be more rational to combat the dehydration of diarrhea with a combination of dextrose and electrolyte solutions. The essentially similar trend in absorption observed in those subjects who received dextrose parenterally and those who did not would suggest the over-all validity of the procedure followed in the study.

Ash: In all cases, there was an increase in fecal ash when more food was given, but this increase was more than covered by the augmented intake resulting in higher absorption values. Thus the higher intake resulted in a net gain to the child.

Sodium: In all cases, the sodium output of the feces was large while the corresponding output in the urine was small, indicating marked conservation of the mineral on the part of the body. The loss of base, particularly sodium, from the stools in diarrhea is well known. That such losses are repaired considerably by feeding more is clearly shown by the data. Increasing the sodium intake either reduced the net loss of sodium or converted a negative balance of sodium into a positive one. The negative absorptions which remained in some patients even with full oral intakes, indicate the need of supplementary sodium either per os or parenterally.

Potassium: Potassium, too, is absorbed from the intestine in amounts roughly proportional to the amount offered. With the exception of Cases 22 and 26 on a low intake, positive absorptions resulted from even the smallest intakes. This would suggest wider use of the oral route for potassium administration.

Calcium: In the normal infant fed on cow's milk practically all of the calcium offered for excretion appears in the stool and amounts to roughly two-

thirds the intake.⁹ In severe diarrhea as much as 90 per cent of the intake may be excreted in the stool, as is shown in our data. There was, however, a net gain in absorption as larger feedings were given in all the cases studied.

Chloride: A considerable amount of chloride is excreted by way of the stools in diarrhea. As is the case with sodium, this loss is appreciably repaired as more food containing chloride is given; however, a supplementary intake appears to be necessary in most instances.

Fat: Whereas the absorption of fat from the intestine of the normal infant amounts to 85 to 90 per cent of the intake, 60 per cent or less is absorbed in severe diarrhea.⁹ Our data show levels of fat absorption varying from 27 to 72 per cent of the intake. The percentage absorption is not greatly affected by the quantity ingested, and it is therefore evident that a high food intake brings about a greater absolute amount of fat absorbed. This is particularly significant in view of the prevalent use of low fat formulas in the treatment of diarrhea, a regimen which may contribute to nutritional failure.

Nitrogen: In the normal infant, about 90 per cent of the nitrogen intake is absorbed. It was observed by Holt, and his associates⁹ that loss of fecal nitrogen even in severe diarrhea is proportionally less than fat and that the percentage of nitrogen intake absorbed rarely falls below 75 per cent. We observed considerably lower values in some of our patients, the percentage absorption in one instance being as low as 27 per cent. As with the other components of the food, the larger intakes induced a larger absolute amount of nitrogen absorbed.

Stools: It is a common observation that the restriction of food causes diminution of the frequency and volume of stools in acute diarrhea. This coincides with our experience in these cases. If the frequency and volume of the stools were used as the criteria of successful therapy, one might well conclude that feeding exerted a deleterious effect on the diarrhea and that the more one starved the more successful was the treatment. I wish to point out again that it is the infant rather than the stools who should be the main concern, and the data herein presented have shown that the infant gains rather than loses with increased feedings even though this is accompanied by an increase in stool bulk. Case 27 illustrated this point very effectively. On a normal full diet twenty watery stools weighing a total of 383 Gm. were passed, in contrast to five watery stools weighing 186 Gm. when the infant was placed on complete oral starvation. From the metabolic data, however, it is evident that appreciable losses of mineral, fat, and nitrogen occurred when nothing was introduced by mouth, while substantial absorptions of all the food components except sodium and chloride took place when a full calorie diet was fed.

The comparison of these six infants on high and low food intakes indicates clearly that the more food that is given by mouth, the greater is the absolute loss of each food constituent in the stool. The stools are increased in volume and frequency as a result of the high feeding, which apparently causes an exacerbation of the diarrhea. It is equally clear, however, that the child absorbs more of each food ingredient as the food intake is increased. By that criterion he is better off, regardless of the appearance of the stools. Even in the severest diar-

rhea we observed no net loss of any food constituent due to washing-out of digestive secretions which had been stimulated by the increased food intake.

In regard to the clinical appearance of the infants, we cannot say with assurance that this was favorably affected during the short periods of liberal feeding. On the other hand, we observed no untoward changes in clinical appearance directly associated with the high feedings. We are inclined to think that longer periods of observation are needed on the two regimes in order to detect clinical differences.

These studies indicate clearly that effective intestinal absorption of all foodstuffs occurs even in the severest of diarrheas and that the absorption is roughly proportional to the intake. Unless it can be shown that a high intake is in some way deleterious or delays recovery (a matter that will be considered in the succeeding paper), it would seem desirable to feed such infants liberally and to disregard the appearance of the stools.

SUMMARY

The absorption of nitrogen, fat, total ash, sodium, potassium, calcium, and chloride has been followed in six subjects with infantile diarrhea on normal and on reduced food intakes. It was found that absorption of each food ingredient was improved on the higher intakes, even though the fecal loss was increased.

From the point of view of absorption it would seem desirable not to restrict food in infantile diarrhea.

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THE EFFECT OF EARLY ORAL FEEDING VERSUS EARLY ORAL STARVATION ON THE COURSE OF INFANTILE DIARRHEA

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IN THE preceding paper reasons were given for questioning the value of the time-honored procedure of early therapeutic starvation in cases of infantile diarrhea, and evidence was presented pointing to the value of early oral feeding. It was shown that even in very severe cases the retention of electrolytes, fat, and nitrogen was improved by feeding. There remained the question of the effect of early oral feeding on the course of the diarrhea. The limited amount of clinical material available at Bellevue Hospital would not permit a convincing answer on this point. We therefore sought an opportunity to study this question in some place where infantile diarrhea was prevalent and where a large controlled series of observations could be made on the duration of the disease in patients treated alternately by early therapeutic starvation and by early oral feeding.

Such an opportunity presented itself in the summer of 1947 through the courtesy of Dr. Ivan Hečko, who invited one of us (A. W. C.) to Bratislava to collaborate in a diarrhea study. The present report deals with a series of 115 patients of whom fifty-five were treated by the conventional regime of early oral starvation and sixty by full calorie feedings from the start.

The nature of the diarrhea which prevails in Bratislava every summer is not clearly established. Previous observations made by the University Bacteriological Institute had indicated that bacillary dysentery played a negligibly small part. This was confirmed during the period of the present study. Two and sometimes three stool cultures were made on all but four patients. In only four instances out of 111 were *Shigella* organisms recovered. *Paraeolon bacilli*, *Proteus vulgaris*, and *Bacillus pyocyaneus* were occasionally isolated but apparently were of little etiological significance. A careful search for parenteral infection was made in every instance, but it was present in less than one third of the cases. It is possible that the unsanitary milk supply played a part in the etiology due to overgrowth of saprophytes, a factor thought to be responsible for "summer diarrhea" in the United States in years past. Raw cow's milk is in common use in Czechoslovakia. A virus etiology must also be considered, but this was not investigated.

PROCEDURE

All patients with diarrhea were admitted to the ward. Alternate patients were offered full feedings from the start, the remainder being placed on a regime of oral starvation.

From the Department of Pediatrics, New York University, Dr. L. Emmett Holt, Director, and the University Children's Clinic, Bratislava, Czechoslovakia, Dr. Ivan Hečko, Director. The expenses of this study were defrayed in part by grants from the John and Mary R. Markle Foundation and from American Relief for Czechoslovakia, in part by the Ministry of Health of Czechoslovakia.

The correction of shock, dehydration, and acidosis received immediate attention in all cases. Plasma (reconstituted from the dried state) was administered by intravenous push infusion in all cases of shock. Acute dehydration was repaired by a solution of equal parts of 10 per cent dextrose and physiologic saline. When clinical acidosis was present, a 5 per cent solution of sodium bicarbonate was added to the dextrose-saline mixture. The total amounts of the various fluids administered were dictated by clinical judgment rather than by laboratory data, as equipment for the latter was lacking. Ten per cent dextrose and 3 per cent Amigen containing electrolytes* were used intravenously to support nutrition in those infants who were not able to take food by mouth for prolonged periods.

After the initial parenteral fluid therapy, the patients placed on the therapeutic starvation regime received water by mouth for twenty-four to forty-eight hours, followed by small feedings of a formula composed of powdered milk, sugar, and water. The formulas were made up so that their concentrations were isocaloric with breast milk, with one-third of the total calories in the form of sugar. Analysis showed that with the exception of a somewhat lowered protein content the composition of the powdered whole milk used in this study was essentially the same as that used in the United States. Intake in the starved group began with amounts equivalent to 20 calories per kilogram of body weight and was increased at the rate of 20 calories per kilogram of body weight daily, or less frequently, depending on the nature of the stools. If, for example, the stools increased in frequency or became very loose, the formula was decreased by 20 or 40 calories per kilogram of body weight and increased slowly once again when the stools improved. Clinical evidence of dehydration was corrected with extra water by mouth or by parenteral saline and glucose.

The full feeding regime consisted of formulas made up of the same materials and concentrations as used in the starved group but in amounts equivalent to 80 calories per kilogram of body weight for infants over 6 months of age and 100 to 120 calories per kilogram for those under 6 months of age. The feedings were started as soon as possible after reparative parenteral therapy was under way, and were continued regardless of the nature and frequency of the stools until complete recovery took place. Only if the infant refused or vomited were feedings omitted and parenteral fluids substituted, but the infant was put on the same full feeding as soon as vomiting or refusal subsided. It was found that less than 10 per cent of the infants in the entire series refused or vomited once the initial state of dehydration, acidosis, and mineral loss was in some measure corrected. As in the starved group, water deficits not made up by the oral route were replaced parenterally. The principal differences between the two regimes lay not only in earlier feeding but feeding with full calories from the very onset. Chart 1 illustrates graphically these differences in intake. From the area between the two curves it may be computed that the fed group received 40.6 per cent more food during the first week than did the starved group.

*Supplied by the courtesy of Mead Johnson & Company, Evansville, Ind.

Sulfathiazole and penicillin were used in all cases where they were believed to be of value in treating complicating infections. Sulfaguanidine was given equally to the first fifty patients in both groups but not to the rest.*

One cubic centimeter of crude liver extract was given intramuscularly to all patients in both groups on admission.

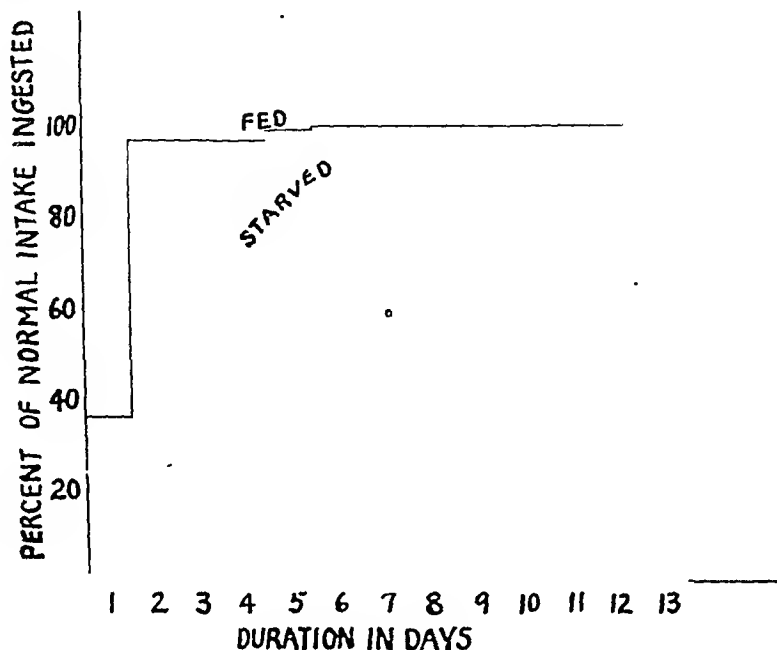


Chart 1.—Per cent of normal intake ingested per day in starved and fed groups. Normal intake: 100 calories per kilogram in infants under 6 months; 80 calories per kilogram in infants over 6 months.

Specimens from the first two stools (and often a third) were collected from the diaper and placed in freshly prepared tetrathionate enriching media and sent by messenger to the University Bacteriological Institute. The material was then incubated and plated on s.s. agar, from which colonies were identified by the usual accepted procedures.

RESULTS

A total of 115 patients were observed in all. There were twelve fatalities, resulting in a mortality of 10.4 per cent. Two deaths were in infants who were taken out of the hospital without consent and were reported as having died at home. The remaining ten were all autopsied. Acute complications such as lateral sinus thrombosis and peritonitis resulted in two early deaths; however, the majority died after a long drawn-out course with malnutrition, complicating infection (particularly purulent otitis media), inanition, and finally terminal collapse. Autopsies on these patients, as expected, were not revealing. Although

*Evaluation of the efficacy of sulfaguanidine in the treatment was not possible because observations on alternate controls without drug were not made.

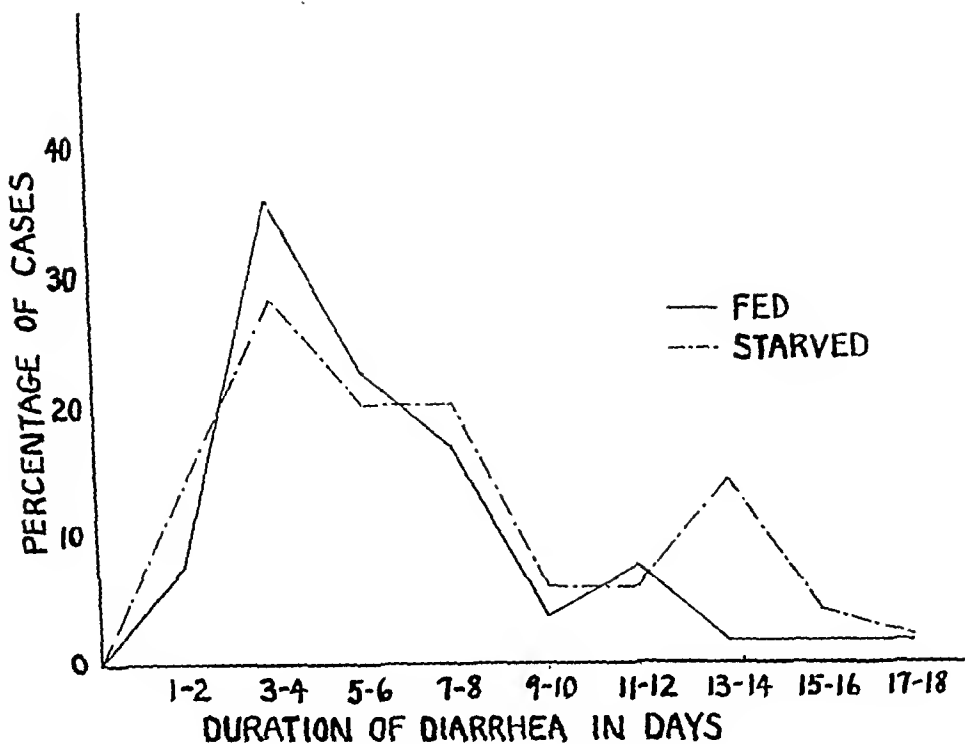


Chart 2.—Distribution curves showing duration of diarrhea with oral feeding and oral starvation.

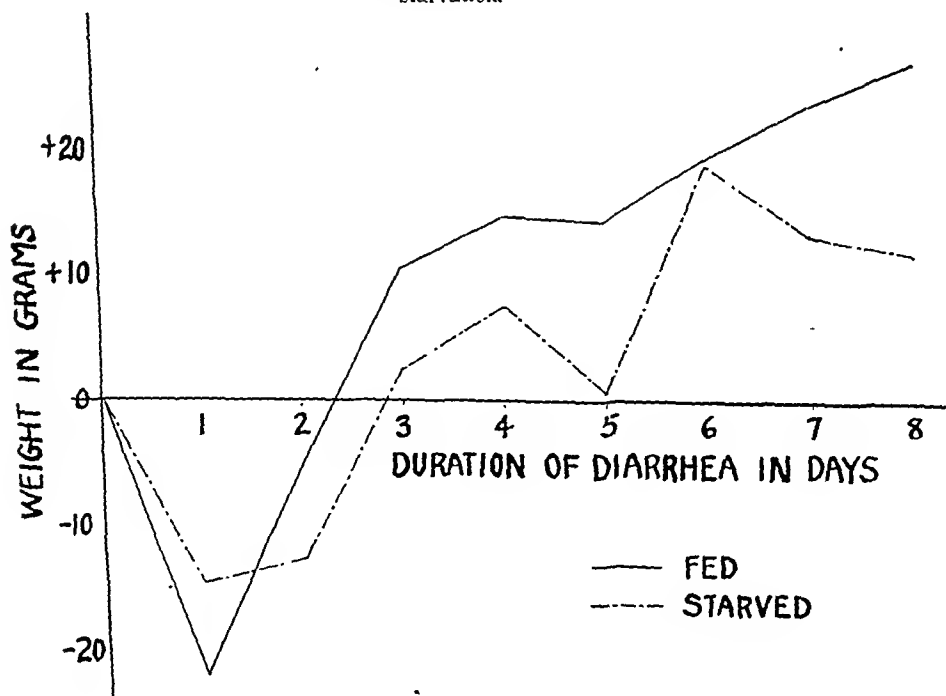


Chart 3.—Composite weight curves showing average algebraic sum of daily weight gains and losses.

TABLE I. ORAL STARVATION

CASE	AGE (MO.)	INITIAL WT. (KG.)	DURATION OF DIAR- RHEA (DAYS)	STOOL CULTURE	COMMENT
1	9	6.54	4	Neg. for dysentery	Moderate dehydration
4	8	4.62	8	Neg. for dysentery; <i>P. vulgaris</i>	Premature; condition fair
6	7	7.00	7	Neg. for dysentery; <i>P. vulgaris</i>	Acidosis, shock, dehydration
8	8	6.40	4	Neg. for dysentery; <i>P. vulgaris</i>	General condition fair
10	2	2.10	6	Neg. for dysentery	Emaciation, marked dehydration
12	23	7.00	7	Neg. for dysentery	Emaciation, rickets
14	4	3.84	11	Neg. for dysentery; <i>P. vulgaris</i>	General condition fair
18	13	8.00	5	Neg. for dysentery	Malnutrition
20	12	8.94	7	Neg. for dysentery	General condition fair
22	12	5.60	3	Neg. for dysentery; <i>P. vulgaris</i>	Marked emaciation
24	5	4.58	6	Neg. for dysentery	Purulent otitis media (<i>Staph. aureus</i>)
26	5	6.05	6	Neg. for dysentery	Shock, dehydration, acidosis
28	22	7.80	4	Neg. for dysentery	Acidosis, dehydration
30	4	4.39	4	Neg. for dysentery	Malnutrition, dehydration
32	2	4.30	4	Neg. for dysentery	Severe dehydration
34	2	3.55	8	Neg. for dysentery	Severe shock, acidosis, dehydration
36	7	5.35	6	Neg. for dysentery	General condition good
38	6	4.80	7	Schmitz bacillus	Emaciation, dehydration
39	12	5.20	13	Neg. for dysentery	Purulent otitis media (pneumococci)
40	11	5.70	7	Neg. for dysentery	Emaciation, dehydration
42	7	5.40	6	Neg. for dysentery	Shock, severe dehydration
42*	7	5.32	3	Neg. for dysentery	Relapse due to otitis media
46	16	8.80	13	<i>Shigella flexneri</i>	General condition fair
48	18	10.70	9	Neg. for dysentery	Primary tuberculosis
51	9	9.80	3	Neg. for dysentery	General condition good
53	8	6.10	16	Neg. for dysentery	Relapse due to otitis media (pneumococci)
59	2	4.21	14	Neg. for dysentery	Relapse due to pharyngitis
61	10	7.80	8	Neg. for dysentery	General condition fair
63	6	6.60	4	Neg. for dysentery; <i>P. vulgaris</i>	General condition fair
65	7	7.80	5	Neg. for dysentery	General condition good
67	6	7.25	5	Neg. for dysentery	Pharyngitis, moderate dehydration
69	6	4.00	10	Neg. for dysentery	External otitis, dehydration
71	9	7.80	4	Neg. for dysentery	General condition fair
73	9	5.25	5	Neg. for dysentery	Emaciation, dehydration, purulent otitis media
75	8	7.40	8	Neg. for dysentery	Shock, severe dehydration
77	7	6.40	3	Neg. for dysentery	Shock, dehydration, otitis media
79	3	4.36	11	Neg. for dysentery	Acidosis, dehydration, otitis media (pyocyaneus)
83	5	5.64	13	Neg. for dysentery	Pyuria (<i>pyocyaneus</i>)
85	9	7.00	7	Neg. for dysentery	Pyuria (<i>B. coli</i>)
87	4	4.90	3	Neg. for dysentery	Shock, severe dehydration
89	2	3.94	4	No culture done	Shock, severe dehydration
91	8	6.16	16	Neg. for dysentery	Bronchopneumonia, otitis media
93	12	6.70	5	Neg. for dysentery	Severe dehydration
95	12	7.50	10	Neg. for dysentery	Acute bronchitis

*The prime (') indicates patients who suffered a relapse of the diarrhea after at least one week's remission.

TABLE I—CONT'D

CASE	AGE (MO.)	INITIAL WT. (KG.)	DURATION OF DIAR- RHEA (DAYS)	STOOL CULTURE	COMMENT
97	12	6.52	18	Neg. for dysentery	Otitis media, moderate dehy- dration
99	2	4.00	4	No culture done	Pyodermia, condition fair
101	4	4.68	14	Neg. for dysentery	Congenital syphilis
105	5	6.80	14	Neg. for dysentery	Purulent otitis media (<i>Staph.</i> <i>aureus</i>)
107	4	4.40	14	Neg. for dysentery	Shock, acidosis, dehydration, purulent cervical adenitis.
109	4	3.80	11	<i>Shigella flexneri</i>	Shock, acidosis, dehydration purulent otitis media (<i>strep.</i> <i>tococi</i>)
Average for total					
50 cases	7.9	5.97	7.8		

seven deaths occurred in the fed group and five in the starved group, the series was too small to make deductions as to the relation of oral therapy to death. The clinical impression was that it played little if any role whatever.

Excluding the twelve fatalities, observations on fifty patients treated by oral starvation and fifty-three by oral feeding are tabulated (Tables I and II).

A. Duration of Diarrhea.—It was evident that certain criteria had to be set up to define the state of recovery from diarrhea to which both groups must adhere. These criteria were: (1) absence of diarrheal stools on a normal intake of food by mouth, and (2) gain in weight not dependent on parenteral fluids which persisted for at least one week. The minimum number of days after admission when both criteria were satisfied was regarded as the time required for recovery from diarrhea, i.e., the duration. Relapses were considered separate cases if they occurred after a full week's remission. These cases are represented in the table by a number accompanied by a prime (''). From the tables the average duration of diarrhea was 7.8 days for the fifty patients in the starved group and 6.1 days for the fifty-three patients in the fed group. The difference between the two figures is not statistically significant. Distribution curves showing duration of diarrhea with oral feeding and starvation are plotted in Chart 2.

B. Weight Gains or Losses.—Chart 3 shows composite weight curves for the two groups. The data were derived from the average algebraic sum of the daily weight gains or losses up to the eighth day of hospitalization. Discharges after the eighth day lowered the number of the original series in both groups so further data would not have been significant. Although the average drop in weight on the first day was slightly greater in the fed group, this group subsequently showed a progressive weight gain which was greater than in the starved group.

C. Stools.—Although the volume of stool was not measured, the clinical impression was that the stools of those in the fed group were much larger and contained more solid matter than those obtained from the starved group. This observation has been substantiated by measurements of stool volumes in the metabolic studies reported in the previous paper. As was pointed out there, the

TABLE II. ORAL FEEDING

CASE	AGE (MO.)	INITIAL WT. (KG.)	DURATION OF DIAR- RHEA (DAYS)	STOOL CULTURE	COMMENT
2	1	2.10	6	Neg. for dysentery	Emaciation, dehydration
3	8	4.50	7	Neg. for dysentery; <i>P. vulgaris</i>	Premature; condition fair
3*	8	4.50	12	Neg. for dysentery; <i>P. vulgaris</i>	Relapse, cause?
4'	8	4.50	11	Neg. for dysentery	Relapse due to pharyngitis (pneumococci, streptococci)
5	8	4.50	7	Neg. for dysentery	Congenital syphilis, malnutrition
7	6	7.00	6	Neg. for dysentery; Paracolon bacillus	Shock, severe dehydration
9	12	5.90	6	Neg. for dysentery	Severe malnutrition
11	8	6.76	3	Neg. for dysentery	Moderate dehydration
13	14	7.90	6	Neg. for dysentery; <i>P. vulgaris</i>	Severe dehydration
15	3	3.95	3	Neg. for dysentery; <i>B. pyocyaneus</i>	Harelip, moderate dehydration
16	2	3.55	5	Neg. for dysentery	Apathy, severe dehydration
17	16	9.00	4	Neg. for dysentery	General condition fair
19	6	5.10	4	Neg. for dysentery	General condition good
21	4	5.10	8	Neg. for dysentery	Mastoiditis (pneumococci), dehy- dration
23	9	7.30	15	Neg. for dysentery; <i>P. vulgaris</i>	Relapse due to otitis media
25	7	5.30	4	Neg. for dysentery; <i>P. vulgaris</i>	Otitis (streptococci) dehydration
27	8	8.10	6	Neg. for dysentery; <i>P. vulgaris</i>	Acidosis, dehydration; otitis media
29	8	8.15	4	Neg. for dysentery	General condition fair
31	5	3.25	2	Neg. for dysentery; <i>P. vulgaris</i>	Emaciation, dehydration
33	2	3.90	2	Neg. for dysentery	Malnutrition, dehydration
35	4	3.10	3	Neg. for dysentery	Emaciation, severe dehydration
37	6	6.00	2	Neg. for dysentery	General condition good
40'	11	5.88	7	Neg. for dysentery	Relapse due to pharyngitis
41	9	7.80	7	Neg. for dysentery; <i>P. vulgaris</i>	Severe dehydration
45	11	6.00	11	Neg. for dysentery	Apathy, moderate dehydration
47	10	7.60	3	Neg. for dysentery	General condition fair
50	2	3.55	6	Neg. for dysentery	Emaciation, chronically ill
52	5	4.65	8	Neg. for dysentery; <i>B. pyocyaneus</i>	General condition fair
54	10	5.60	4	Neg. for dysentery	Bronchopneumonia; condition poor
60	7	5.50	4	Neg. for dysentery	Relapse at home, cause?
64	5	3.90	6	Neg. for dysentery	Acidosis, dehydration, cervical adenitis incised and drained.
64'	5	4.32	8	Neg. for dysentery	Relapse due to inadequate drainage?
66	5	5.43	4	Neg. for dysentery	Pyuria (<i>B. coli</i>)
70	12	9.00	2	Neg. for dysentery	Shock, dehydration, acidosis, purulent otitis media (pneu- mococci)
72	7	5.75	6	Neg. for dysentery	Shock, severe dehydration
74	5	4.30	4	Neg. for dysentery	Malnutrition, rickets?
76	7	5.30	12	Neg. for dysentery	Shock, dehydration, otitis media abscess of thigh (<i>pyocyaneus</i>)
78	1	2.70	3	Neg. for dysentery	Shock, severe dehydration
80	4	3.80	5	Neg. for dysentery	Admitted in extremis, dehy- drated; stormy course

*The prime (') indicates patients who suffered a relapse of the diarrhea after at least one week's remission.

TABLE II—CONT'D

CASE	AGE (MO.)	INITIAL WT. (KG.)	DURATION OF DIAR- RHEA (DAYS)	STOOL CULTURE	COMMENT
80	4	3.60	7	Neg. for dysentery	Relapse due to too early discharge?
82	5	6.90	18	Neg. for dysentery	Severe dehydration bronchopneumonia, purulent otitis media (<i>pyocyaneus</i>)
84	14	7.60	5	Neg. for dysentery	Acidosis, severe dehydration
86	5	5.00	7	Neg. for dysentery	Moderate dehydration
88	12	5.50	10	Neg. for dysentery; <i>P. vulgaris</i>	Malnutrition, moderate dehydration
90	5	6.04	4	No culture done	Shock, severe dehydration
94	10	8.00	3	Neg. for dysentery	General condition fair
96	15	8.40	3	Neg. for dysentery	Lobar pneumonia, dehydration
98	6	5.59	4	Neg. for dysentery	Otitis media (streptococci), dehydration
100	5	5.65	14	No culture done	General condition fair
102	3	3.14	3	Neg. for dysentery	General condition fair
104	8	9.00	3	Neg. for dysentery	General condition fair
106	24	6.20	10	Neg. for dysentery	Otitis media (pneumococci), severe dehydration
108	2	3.65	6	Neg. for dysentery	Shock, severe dehydration
Average for total					
53 cases	7.3	5.56	6.1		

increase in stool volume incident to feeding is not a contraindication to the giving of oral food; on the contrary, more food is absorbed when the infant is on an oral feeding regime despite the increased loss in the stools.

COMMENT

The data presented indicate that early oral starvation, although it improves the appearance of the stools and decreases their frequency, fails to shorten the course of the diarrhea; actually the course in the starvation group was a trifle longer. The difference, however, does not appear to be statistically significant, and we are inclined to conclude that the duration of the digestive disturbance is conditioned by factors unrelated to the food. Since the traditional fear of prolonging digestive intolerance by oral feeding seems therefore to be an unwarranted one, there is every reason for taking advantage of the increased absorption of foodstuffs on a high food intake, which was demonstrated in the preceding paper. It would seem appropriate at this point to recall the statement made a quarter of a century ago by Park:¹ "The habit of starving an infant just because he has frequent stools is fallacious and gives rise to disastrous results. I have often thought in retrospect that many infants on our wards might have been fed more successfully if the stools had been totally disregarded."

In reaching the conclusion that the oral route should be used to the greatest extent in infantile diarrhea, we wish to emphasize that we are not urging it as a substitute for parenteral electrolyte or food administration. The gains which have resulted from the latter in recent years are far beyond the realm of dispute. Our point is that the best of parenteral therapy today has its shortcomings, and

for this reason the oral route should be employed as far as possible. By this means the patient's nutrition is best maintained, and it is to be hoped that some of the results of late nutritional failure can be avoided. In this respect an analogy between the treatment of diarrhea and that of typhoid fever may be drawn. The philosophy of supporting nutrition in the typhoid patient by a liberal, high caloric, low roughage diet was a radical departure from the accepted therapy when first introduced by Coleman² and Dubois,³ but the clinical results of a generation have demonstrated the basic soundness of this approach.

Attention should be called to the limitations of early oral feeding. It is obviously impractical in the presence of vomiting. In the case of the acutely dehydrated infant who is being given infusions, the horizontal posture and difficulty in belching the baby necessitate caution in giving bottle feedings, for there is danger of regurgitation and aspiration. Under these circumstances, gavage may be employed with greater safety. It is our experience, however, that vomiting rarely causes difficulty once the infant is brought out of the stage of dehydration, shock, and acidosis.

SUMMARY

Data have been presented on 115 patients with infantile diarrhea studied at the University Children's Clinic, Bratislava, Czechoslovakia. Of this group, twelve died, a mortality of 10.4 per cent. The remaining 103 patients were divided alternately into those fed full calories at the onset and those on therapeutic oral starvation. The duration of the diarrhea was not prolonged under the feeding regime. There was a more prompt and consistent weight gain in those who were fed, in spite of the larger volume of stool excreted.

The evidence presented by this clinical study substantiates the metabolic findings of the preceding paper that it is advantageous to feed the infant early with full calories in diarrhea rather than to follow the conventional treatment of oral starvation.

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A SIMPLE FORMULA FOR PREMATURE AND FULL-TERM INFANTS

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THE need for a simple milk formula for babies is great. Such a formula would simplify not only the care of the baby at home, but it would do a great deal to remove the confusion that exists in the average hospital where many doctors prescribe individual formulas for their patients. Such confusion in the formula room breeds inefficiency and increases the chances for error in preparation. Bacterial contamination is also much more likely under such circumstances.

Simple routines in patient and hospital care were a necessity at the U.S. Naval Hospital in San Diego because of the transitory and often inexperienced personnel as a result of war conditions. It was, therefore, thought that standardization and simplification of the milk formula used for babies and infants in the hospital would help a great deal in solving this problem.

STUDY

The purpose of this paper is to report the use of the simplest formula possible—namely, equal parts of evaporated milk and water.* This formula was used for fifty-six consecutive premature and approximately 700 full-term infants at the U. S. Naval Hospital in San Diego, over a one-year period. No carbohydrate was added to the formula because it was thought that carbohydrate increases colic, and recent studies have shown that most carbohydrates are rachitogenic.¹ The milk was not diluted below whole milk concentrations because recent studies have shown that premature infants thrive better on a high protein formula. (Whole cow's milk has 3.5 per cent protein as compared with 1.5 per cent protein in human milk.²)

In most instances the infants were fed nothing for the first twelve hours of life. During the next twelve hours they received 5 per cent glucose in distilled water. The mixture of equal parts of evaporated milk and water was begun on the second day of life and was given without change in most instances until the infant was 5 months of age. After 5 months most of the babies were put on plain cow's milk. All premature infants weighing less than $4\frac{1}{2}$ pounds were routinely fed by gavage tube. In many instances infants weighing between $4\frac{1}{2}$ and 5 pounds had to be gavage-fed also. These gavage feedings were maintained until the infants exhibited a strong sucking reflex, at which time a gradual introduction of bottle feedings was begun. The amount of formula given was determined primarily by the infant's ability to retain his feedings and roughly by 150 to 200 c.c. per kilogram of body weight per day divided into eight three-hour feedings. Two very small infants were fed every two hours.

Read before the San Diego County Medical Society, Dec. 9, 1947.

*This formula is similar to plain whole cow's milk except that it is sterile, homogenized, and in most instances is fortified with vitamin D.

Parenteral fluids were rarely used. In instances when a prominent anemia developed, blood was given intravenously in amounts of 20 c.c. per kilogram of body weight. Vitamin therapy was begun in the premature infants at 3 weeks of age; a water-soluble preparation containing A, B₁, B₂, C, and D was given. Iron was not used routinely, but when given, ferrous gluconate was used. Solid foods were instituted beginning about the second month of age in the larger premature infants and in all full-term infants. The usual order of introduction of solid foods was: cereal, vegetables, fruits, meat, and eggs. By 5 months of age, most infants were taking these foods well.

For several reasons, the premature infants seemed to be the best group in which to study the effect of this simple mixture in more detail, although the full-term infants were fed the same formula. First of all, the premature infants remained in the hospital for a longer period of time. This helped to eliminate the personal factor of an apprehensive mother who was willing to attribute every strange occurrence in the baby to the new formula. Secondly, the nursing care was more personal in the premature infant nursery, and as a result better records were kept as to the number and nature of the stools, the response of the baby to the formula, and the daily weight. Thirdly, it was felt that in all probability if the premature infants thrived on the formula the full-term infants would do likewise.

RESULTS OF STUDY

We were able to use the simple mixture of equal parts of evaporated milk and water routinely in all premature infants beginning on the second day of life with surprising success. In not a single instance did we have to resort to a change in the formula in the premature infants because of intolerance to the mixture. One premature infant who was transferred from an outside hospital had twelve loose stools the first day on the formula. This infant was given glucose water during the next twenty-four hours and then the formula was started again. No more loose stools were noted in this infant, and he gained weight well.

Most of the infants tended to have slightly more formed stools than the average newborn infant on a standard formula. Constipation, however, was observed in only two infants, and it lasted for only one day; no change in the diet was required. The number of stools per day varied from one to eight, and the average was five stools per day. None of the infants displayed an intolerance to the amount of fat contained in the formula unless the number of stools could be considered abnormal.

As seen by the charted weights (Figs. 1-6), all fifty-six premature infants gained weight well on the formula. Several infants had no physiologic weight loss, and the majority had only a small weight loss. The average premature infant in this series regained his birth weight in twelve days and was discharged from the hospital in twenty-seven days.

By definition (all infants weighing less than 5½ pounds), there were actually seventy-five premature babies born during the period of this study.

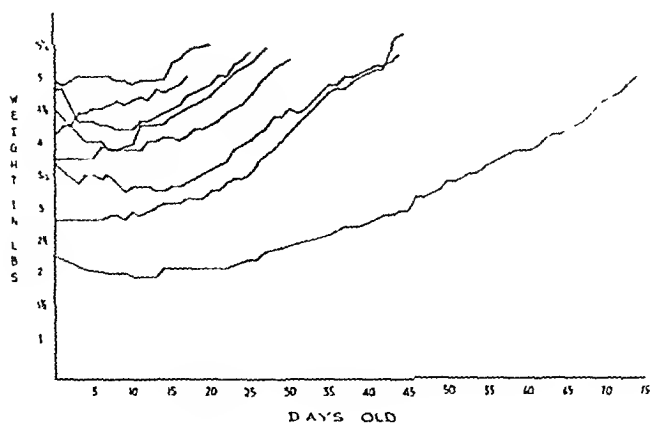


Fig. 1

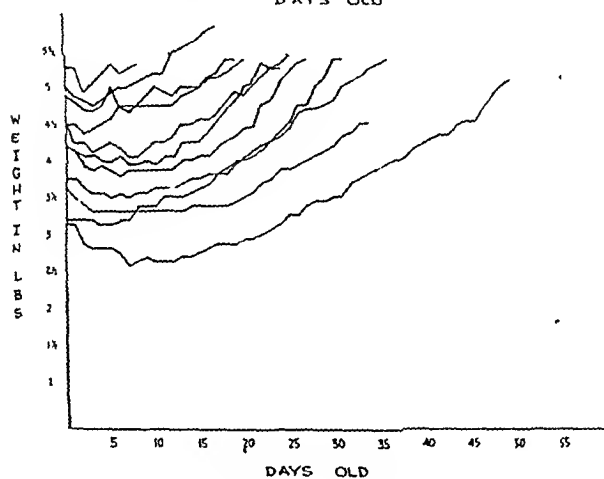


Fig. 2.

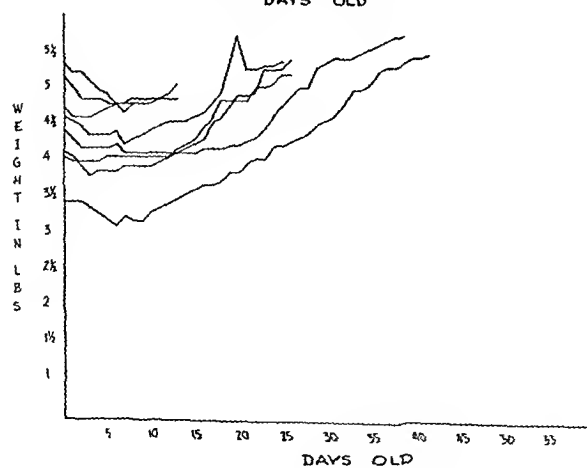


Fig. 3.

Figs. 1-3.—Graphs showing the daily weights of the fifty-six premature infants fed equal parts of evaporated milk and water.

Fig. 4

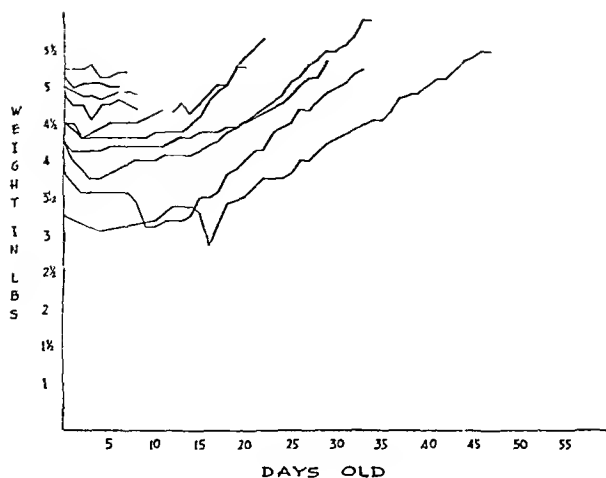


Fig. 5.

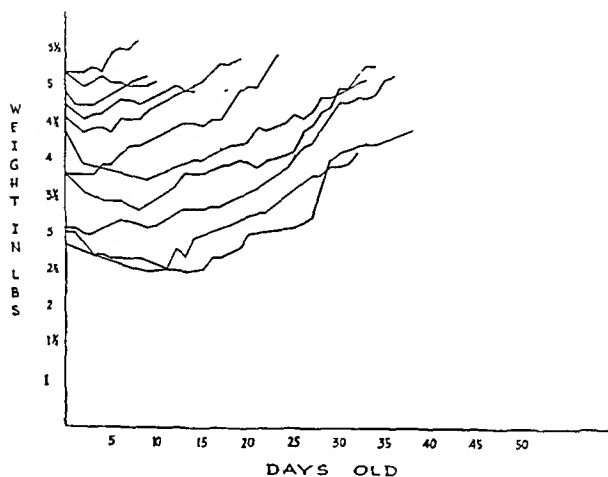
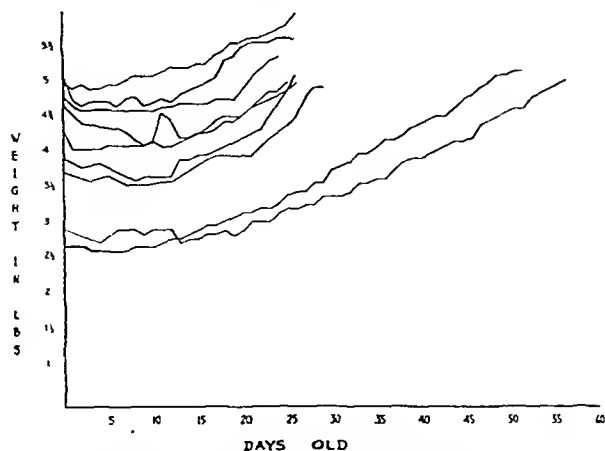


Fig. 6.



Figs. 4-6.—Graphs showing the daily weights of the fifty-six premature infants fed equal parts of evaporated milk and water.

Only fifty-six of these were admitted to the premature infant nursery. Ten of the remaining nineteen infants were large and mature enough to be placed in the regular nursery. The other nine babies died. Four of the deaths occurred in babies who were of only five to six months' gestation. Two of the other deaths were twins of six and one-half months' gestation. Two of the premature infants eventually developed an idiopathic hydrocephalus and were still alive at 9 months of age, when last seen. They did well on the formula, and I do not believe there was any association between the hydrocephalus and the diet.

As mentioned previously, this formula was also given to approximately 700 full-term infants, beginning on the second day of life until 5 months of age. Although many mothers were apprehensive and willing to attribute rashes, colic, constipation, and diarrhea to the new mixture, close appraisal revealed that the infants did well on the mixture. On an average, the weight at 6 months was 2 pounds above the median. Once the group psychology came into existence, most mothers welcomed the simple formula and recommended it to their friends. It was not long before the well baby clinic became a counselling center for discussion of the growth and development of infants rather than a diet center as it had previously been.

DISCUSSION

The need for a standard simple formula both in the hospital and home was stressed earlier in this paper. This study, involving fifty-six premature infants and approximately 700 full-term infants, has shown that the simple mixture of equal parts of evaporated milk and water is well tolerated by infants from the second day of life to the fifth month of age. The babies gained weight consistently and did well in every respect.

McCulloch³ and McMahon⁴ have also used evaporated milk without added sugar in infant feeding for several years and feel that it is superior to mixtures with added carbohydrate. Both authors, however, favor changing the ratio of water to milk as the infant matures; I feel that such a change is not necessary in the majority of instances. McCulloch felt that evaporated milk without added sugar "is a suitable food for all normal infants and small children." He likewise suggested the advantage of simplicity in preparation of such a formula over a mixture containing added sugar.

Hess⁵ states in the recent edition of Brennemann that "slower increases in weight may be expected of the artificially fed infant." Actually the premature infants in this study regained their birth weight one to five days earlier and were discharged from the hospital one to two days earlier than those in Hess' series, all of whom were fed breast milk. (See Tables I and II.) Other investigators have shown that slightly altered cow's milk is actually better than breast milk for premature infants.²

The artificial feeding used in these premature infants apparently did not increase the morbidity or mortality rate in this series as suggested by Hess.⁵ The over-all mortality rate in this series was 12 per cent as compared with 27 per cent in Hess' series. One of the premature infants developed bilateral submaxillary gland abscesses, from which a pure strain of *Staphylococcus aureus*

TABLE I. AVERAGE LENGTH OF STAY IN HOSPITAL

BIRTH WEIGHT (LBS. AND OZ.)	DAYS	DAYS (HESS)
2 and 3 to 3 and 5	45.3	45.7
3 and 5 to 4 and 6	30.7	30.5
4 and 6 to 5 and 8	17.7	19.9

TABLE II. AVERAGE DAY ON WHICH BIRTH WEIGHT WAS REGAINED

BIRTH WEIGHT (LBS. AND OZ.)	DAY	DAY (HESS)
2 and 3 to 3 and 5	13.9	18.6
3 and 5 to 4 and 6	12.8	14.4
4 and 6 to 5 and 8	10.8	11.8

was recovered. The infection responded well to penicillin. Except for this one case, no other infections occurred in the premature infant nursery during the study.

This study has convinced me that nearly all premature infants will do well, providing they are constitutionally able to live, if they are given excellent nursing care alone.

SUMMARY

1. There is a great need for a simple formula for infants.
2. The simple mixture of equal parts of evaporated milk and water was used from the second day of life in fifty-six consecutive premature and 700 full-term infants with good results.
3. The premature infants fed this simple formula regained their birth weight earlier and were discharged from the hospital earlier than those in a comparable series.

ADDENDUM

It is significant that such low morbidity and mortality rates occurred in this study. During the period the observations were made, a serious epidemic of diarrhea of the newborn infant with a high mortality rate plagued Southern California. Thirty infants in our regular nursery became ill; however, none of the premature infants developed diarrhea.

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PROSPECTS FOR PREVENTION OF CHRONIC BRONCHITIS AND BRONCHIECTASIS

RATIONAL MANAGEMENT OF BRONCHOPULMONARY INFECTIONS BY PENICILLIN AEROSOL THERAPY

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THE common background of chronic bronchitis and bronchiectasis is, in the majority of cases, chronic nontuberculous bronchopulmonary infection. Although the pathogenesis of bronchiectasis is still a matter of controversy, it seems to be well established that dilatation of bronchi may originate from those same illnesses which frequently initiate chronic bronchitis. It appears reasonable, then, to base a discussion of possible prevention of chronic nontuberculous pulmonary disease on the etiological features common to simple chronic bronchitis and bronchiectasis: Pyogenic respiratory infection of a primary character as in tracheobronchitis, or when secondary to such virus diseases as measles or influenza, is an important factor in bronchial suppuration with subsequent bronchial obstruction and atelectasis. These changes, reversible in the beginning, may lead to chronic pulmonary disease with fibrosis, emphysema, and bronchiectasis¹⁻³ (Table I).

This type of respiratory illness is very common; its actual incidence can be estimated only if it is realized that conditions diagnosed and indexed as acute bronchitis, grippe, and pneumonia frequently are but exacerbations of a fundamentally chronic disease.

The economic loss due to chronic bronchitis and bronchiectasis is enormous, expressed in missed working days and millions of dollars spent for more or less effective therapeutics. The suffering of many patients affected by these illnesses is great. The irregular school attendance of children in whom the diseases are developing only foreshadows the semi- or complete invalidism of many of them in later years.

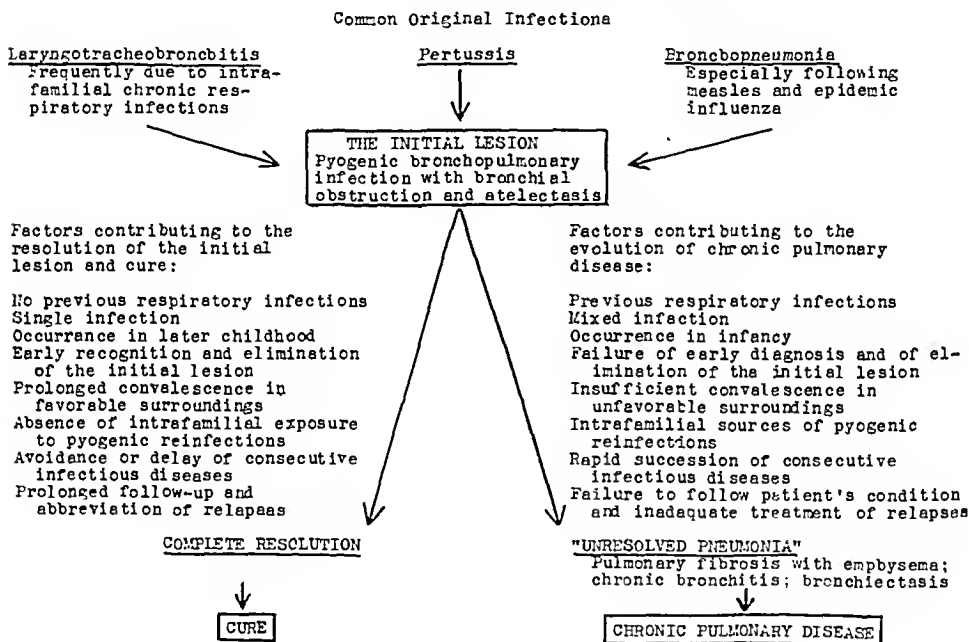
It is true that in recent years the previous complacency toward this type of pulmonary ailment has changed to a more active approach. Chemotherapy and antibiotics give temporary help in many cases of chronic bronchitis, and successful surgical intervention in patients with bronchiectasis restores health in an increasing number of cases.

Great as these advances are, they do not solve the urgent problem of preventing chronic bronchopulmonary infections. Although the belief that not much can be done to avoid bronchiectasis still seems to be deep-rooted, a prophylactic approach has for many years been considered by farsighted physicians.^{1, 4-8} They realized that a rational therapy should be based upon knowledge of all etiological factors involved and upon proper therapy of the infectious process in its early stages.

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Most pleas for prevention of the chronic condition have been made by pediatricians or have been directed to them, since, in a high percentage of cases, chronic bronchitis with or without bronchiectasis has its onset in such common childhood diseases as bronchopneumonia (especially following measles) and pertussis.⁵⁻¹² Less appreciated, however, has been the significance of laryngotracheobronchitis as an initiator of pulmonary disease. This severe respiratory illness of early childhood, especially if complicated by bronchiolitis and bronchopneumonia, accounts not only for the death of a great many children, but also for the chronic illness of many more.

Table I: EVOLUTION OF BRONCHOPULMONARY INFECTION



Little attention is given to the most common source of recurrent laryngotracheobronchitis—namely, exposure of children to chronic nonspecific pulmonary infections in the family. Anxious as parents and physicians are to avoid any contact of children, especially of infants, with sufferers from banal acute respiratory infections, the danger for such children in being exposed daily to a relative affected by chronic respiratory illnesses other than tuberculosis, is still grossly disregarded. It is the rule rather than the exception to find chronic bronchitis of more or less severe character in one or more relatives of children affected by recurrent attacks of tracheobronchitis and pneumonia. In my experience, which confirms Duncan Leys' observations,⁵ respiratory infections as initiators of chronic pulmonary disease in children under the age of 2, could be traced in at least 70 per cent of cases to conditions of the same type in the family. In this respect, it should be mentioned that, since

the end of World War II, an increasing number of small children have been exposed to pulmonary infections which have developed in members of their families. Many veterans were affected by epidemic respiratory infection while in service. Such illnesses are in many cases now proving of recurrent and even chronic character, thus constituting a continuous source of infection for their children.¹³

The significance of such pulmonary infections in early childhood is best demonstrated by the fact that among thirty-nine children over the age of 2 who had been hospitalized for acute bronchopneumonia, twenty-six had a definite history of recurrent respiratory episodes since infancy (Table II). This merely confirms the general experience that children whose respiratory organs are damaged in the early part of life usually react severely to consecutive infections involving the respiratory tract.

TABLE II. THE POTENTIALLY RECURRENT AND CHRONIC CHARACTER OF BRONCHOPNEUMONIA IN CHILDREN. A FOLLOW-UP ON FIFTY UNSELECTED PATIENTS, HOSPITALIZED FOR BRONCHOPNEUMONIA AND TREATED WITH SULFONAMIDES AND/OR PARENTERAL PENICILLIN

AGE AT TIME OF HOSPITALIZATION	NO. OF CASES	CHILDREN'S CONDITION AFTER TWO YEARS		
		ILL HEALTH; PROGRESSIVE PULMONARY INFECTION	GOOD HEALTH BUT RECURRENT RESPIRATORY INFECTIONS	GOOD HEALTH; NO RECURRENT RESPIRATORY INFECTIONS
Under 2 years of age	11	4	5	2
2-15 years of age with recurrent mild or severe respiratory infections since infancy	26	9	14	3
2-15 years of age without recurrent respiratory infections	13	3	5	5
TOTAL	50	16	24	10

It is true that many children may and do recover completely from pertussis, measles pneumonia, and laryngotracheobronchitis. A number of factors determine to a great extent whether an acute bronchopulmonary infection ends in cure or in chronic illness. Unfavorable factors include occurrence of the initial infection in infancy, subsequent pulmonary infections, lack of adequate treatment, and insufficient convalescence in poor and unhealthful surroundings. Favorable factors include the occurrence of measles pneumonia and pertussis in later childhood without preceding respiratory infections, and an undelayed, proper treatment with prolonged convalescence in a favorable milieu. A discussion of preventive measures against chronic bronchitis and bronchiectasis must take into consideration that only in a minority of cases can such favorable factors materialize. As in tuberculosis, a prophylactic approach should be dictated by the potential danger of the early lesion rather than by the possibility that the lesion may heal spontaneously.

Certain misconceptions regarding the evolution of chronic bronchopulmonary infection impede a rational management. In fact, there is hardly any other condition which is more frequently misinterpreted from the very beginning to its more advanced stages. A critical analysis of current treatments of the acute phase will indicate that by treating pyogenic tracheobronchitis and

bronchopneumonia like pneumococcal pneumonia, the illness is not always conquered. The primarily exudative process of pneumococcal pneumonia usually resolves completely. However, the suppurative process encountered in pyogenic bronchopulmonary infections is, as previously mentioned, an entirely different type of lesion. Short treatments with modern antibacterial substances prove highly effective in alleviating the acute infectious process, but do not regularly prevent a residual infection and continuation of some bronchial suppuration. Where free drainage from the involved bronchopulmonary segment is impaired, the restoration of a normal anatomical and physiologic state is inhibited.

In these instances, a variety of bronchial and peribronchial lesions, frequently labelled "unresolved pneumonia," mark the transition to chronic pulmonary disease. Bronchoscopic examinations¹ and x-ray findings such as mottling of the lungs or atelectasis, indicate that the underlying processes are others than true pneumonic consolidations. The slow disappearance of the lesions paralleled by persistent localized râles in the affected area is sufficient warning that the patient has not actually overcome his illness. The recent tendency to label such pulmonary conditions "atypical pneumonia" or "virus pneumonia" merely because they do not present the features of pneumococcal pneumonia or because they have been initiated by virus diseases, further deflects attention from their potentially chronic character. The consequences of neglecting to follow up these children generally become evident only after many years, when frank bronchiectasis is found at the site of the original infection, or chronic emphysema and pulmonary fibrosis have developed. Occasional observations on the condition of children after their apparent recovery from bronchopneumonia prove that a considerable number of them bear the mark of chronic pulmonary disease after a relatively short period.⁵ Most alarming is the fact that current treatments of bronchopneumonia do not seem to have appreciably changed the situation Leys reported twenty years ago.

Out of fifty children hospitalized in 1945 for bronchopneumonia and treated with sulfonamides and/or penicillin, sixteen presented symptoms and frequently definite signs of subacute or chronic bronchopulmonary infection two years later. About half of these sixteen children had sought medical advice during these two years or had been rehospitalized for more severe relapses, some of them for another attack of bronchopneumonia. Twenty-four others of the fifty children, although apparently in good health, had been affected since their hospitalization in 1945 by relatively mild but recurrent respiratory episodes diagnosed as grippe, cold, and the like. Thus, only ten children of the whole group had remained free from respiratory symptoms during the two years following their bronchopneumonia. (Table II.)

A more detailed analysis of the fifty cases revealed the following: Thirty-nine children were over 2 years old at the time of their hospitalization; in twenty-one of these older children, the bronchopneumonia apparently was of the "primary type": in the remaining eighteen, it was preceded by measles or pertussis. However, in twenty-six of these thirty-nine cases, the history revealed recurrent respiratory episodes, frequently of severe character, since early childhood. It seemed, moreover, that in cases of measles pneumonia and pertussis,

the tendency of the infection to become chronic was more pronounced in a child with previous respiratory infections.

Although these observations concern only a relatively small group, in which, moreover, other variables have not been considered, they indicate the potentially recurrent and chronic character of a condition generally misinterpreted as an acute illness. It also appears that current short treatments with modern antibacterial substances are not the solution. The situation parallels observations on the recurrence of other infections following treatments with sulfonamides and antibodies which frequently mask rather than prevent the development of a chronic condition.

As the bronchopulmonary infection takes its course, sometimes progressing rapidly but more often rather insidiously, proper management, which still could prevent irreparable damage, is frequently delayed by failure to realize the actual character of the disease and by futile therapeutic measures. The relatively good general health of the children and the lack of typical abnormal signs in between the characteristic exacerbations mislead parents and physicians alike. Coughing spells at night or in the morning are at first given scarcely any attention, or it is believed that the child might outgrow the tendency to "colds" or "croup." When, despite use of all available remedies, respiratory symptoms increase, and especially if the parents happen to notice such ominous symptoms as blood-streaked sputum, a chest x-ray is usually taken. In most instances the report "negative for tuberculosis" or "findings indicative of repeated upper respiratory infections" all too often gives the false assurance that no serious condition exists. Fortunately, the fruitless practice of placing children with bronchopulmonary infection in sanatoriums as potentially tubercular has been more and more discarded. Many doctors, however, still concentrate on ruling out tuberculosis, thereby losing sight of other serious pulmonary conditions which, more than tuberculosis, are likely to develop after measles, pertussis, and tracheobronchitis.

Equally grave consequences may result from erroneous evaluation of associated conditions and disguising symptoms as the cause of the disease. Kaiser's observations¹⁴ on tonsillectomized and adenoidectomized children, compared with children not submitted to such surgical intervention, have revealed clearly that the removal of the supposed "focus of infection" in the upper respiratory system actually did not prevent the recurrence of bronchitis and pneumonia. Although a more conservative approach to tonsil and adenoid removal can be noted at present, it is still the exception rather than the rule to find children with chronic bronchitis who have not undergone such intervention. In all the discussions about upper respiratory infection as a cause of chronic pulmonary disease, and vice versa, the following fact has been insufficiently considered. Measles, pertussis, influenza, and other illnesses known to initiate chronic pulmonary infections frequently involve upper and lower respiratory systems simultaneously and leave their mark in both. Therefore it can not be expected that even successful elimination of nose, throat, or sinus infections can prevent the chronicity of an existing infections process in the bronchopulmonary system.

The observations of Kaiser and Perry and King,¹¹ as well as the clinical history of many children seen in the office or clinic, indicate that chronic infection of the lower respiratory system is not infrequently initiated or aggravated by tonsillectomy and adenoidectomy. Therefore, it is imperative that the pediatrician, before giving his consent to these surgical measures, consider all factors possibly responsible for the child's symptoms, especially if the history indicates that such symptoms followed an infection of the lower respiratory tract.

The similarity of asthmatic symptoms in bronchial infections to true allergic asthma is another cause of misinterpretation and delayed rational treatment. Ever since earlier students of asthma emphasized the importance of proper distinction of "organic asthma" from "spasmodic asthma," the differential diagnosis between chronic bronchitis and true allergic asthma has been recognized as an important problem,¹⁵ although it has been the subject of much controversy. In another paper,¹⁶ I have stressed anew the significance of chronic bronchitis as the direct cause of what is variously diagnosed as asthmatic bronchitis, intrinsic asthma, bacterial and infectious asthma. The life history of children with asthma of this type usually indicates that asthmatic manifestations appeared in the course of a developing respiratory infection.¹⁶⁻¹⁹ Such infection generally proves to have been initiated by acute respiratory episodes such as pneumonia, pertussis, or tracheobronchitis, rather than by previous respiratory allergy.¹⁶ Attacks of wheezy dyspnea occurring in these instances can be sufficiently explained by bronchial obstruction due to infectious exudations. The prevalent conception that true allergy usually precedes or follows infectious asthma is not sufficiently substantiated by actual observations. An allergic condition, if found in children with bronchopulmonary infection, may complicate the picture, and if not properly treated, may aggravate the illness as would any other coexisting affection. However, the occurrence of so-called mixed atopic and infectious asthma does not necessarily imply that allergic mechanisms, per se, are responsible for irreversible lesions, which can be found in both allergic and nonallergic persons. Indeed, clinical observations on the etiology of bronchiectasis do not support the assumption of allergy as an appreciable etiological factor of this condition.^{11, 12, 20-22} With regard to proper therapy, it is of secondary importance whether or not one accepts a hypothetical bacterial allergy as responsible for pulmonary infection. Attempts to desensitize a patient to bacterial agents, instead of attacking the invaders directly, are in our day no more rational than was tuberculin therapy for tuberculosis years ago. Nonspecific therapy, especially antibiotics, directed against the infection as such, is now widely applied in chronic asthma with infectious "complications." It is obvious that such treatment would bring more help to the patient if applied before the advanced stage had developed, regardless of whether or not allergy is found or suspected.

From what has been outlined thus far, it appears that a broad approach to the problem of prevention of chronic bronchopulmonary infection is a prerequisite for its possible solution. However, the principal goal remains the

earliest possible eradication of the infectious process. In searching for such therapy, I have found that continuous administration of penicillin at the site of infection by way of inhalation can accomplish more than any other treatment thus far known. Promising results with penicillin aerosol therapy in far-advanced pulmonary infection, initiated the first attempts three years ago to use this method in potentially chronic respiratory infections.²⁶

It is not intended to elaborate in this paper on technical problems of penicillin aerosol therapy, which has been described in numerous publications.²³⁻²⁵ Nevertheless, certain adaptations should be mentioned which are important in using this method for children with subacute and chronic bronchopulmonary infection. In these stages of the disease a treatment for several weeks or even months is required. Therefore, a method of giving penicillin aerosol at home in an efficient way and involving the least possible expense is essential.²⁷

Nebulization by hand bulb is too cumbersome for treatment of any length, and oxygen as the source of pressure too expensive for many patients. A simple bicycle pump proves serviceable for the purpose if a glass-fiber filter is inserted between pump and nebulizer.²⁸ Such a pump can also be used by relatives of young children to fill a head tent, under which the patient breathes in the penicillin. The nebulizers used for aerosolization of the antibiotic are the same as usually recommended for adults. The DeVilbiss No. 40 and Premo are efficient in most cases and are within the means of even patients of the lower income group. The Vaponefrin plastic nebulizer has proved especially helpful for children, both because it is unbreakable and because it reduces the nebulization period. Since it was found that many children preferred to inhale through the nose and exhale through the mouth, rather than vice versa, this mode has, in an increasing number of cases, been applied, using a nasal adapter. The re-breathing bag filled with hot water, recommended by Barach as an accessory, was found to complicate the treatment and was unnecessary in the majority of cases. It was used only if the addition of hot moisture was indicated or if the child lost a considerable amount of penicillin by improper breathing technique when inhaling directly from the nebulizer.

As for the required dosage of penicillin, high doses given at the start of treatment proved most effective in eliminating the active infection. One hundred thousand units of crystalline penicillin as supplied in vials or soluble tablets, administered two or three times daily, frequently accomplished the disappearance of respiratory symptoms within one or two weeks unless the condition was advanced. When the head tent was used, higher dosage was needed to allow for the unavoidable loss of penicillin involved in that method. In mild cases, it was found that one daily inhalation of 50,000 units of penicillin was sufficient to control the infection once it had subsided. In more severe cases, especially in those of long duration, high daily doses had to be continued for several months to assure a more stabilized condition. Since no clinical, roentgenologic, or laboratory methods reliably indicate the actual arrest of a bronchopulmonary infection, the treatment was discontinued only gradually and resumed immediately if respiratory symptoms reappeared.

The still-prevalent fear that prolonged administration of penicillin might produce serious untoward side-effects and might develop penicillin-resistance in the patient, did not seem to be substantiated in this series. Irritation of tongue and pharynx and skin reactions were observed in a number of patients, but were seldom of such severe character as to force discontinuing of the treatment. Rinsing of the mouth and antihistaminic drugs proved most helpful in counteracting side effects. A less prompt response to the antibiotic could in almost all patients be explained by the more serious character of the disease, improper treatment technique, and the like. In none of the patients from whom sputum could be obtained were pathogenic organisms found other than penicillin-sensitive ones. In the remaining patients, a prompt response to high doses of the antibiotic was held sufficient clinical evidence that pyogenic bacteria, such as are commonly found in bronchopulmonary infections, had been the causative agents. No efforts were made to obtain blood levels of penicillin, since high concentration of the antibiotic at the site of infection and not in the blood is the major aim of penicillin aerosol therapy.

An analysis of therapeutic effects of this new method should consider its lasting results rather than merely early responses, spectacular as the latter usually are. Therefore, the tabulation of treated patients includes only children who had been followed up for at least one year. Moreover, the tabulated cases were restricted to children who had been ill for at least three months, and had been previously treated by various other methods without appreciable improvement. Children with acute bronchitis, which usually cleared up after a few treatments, do not appear in this group. Neither do cases of frank bronchiectasis, because the evaluation of penicillin aerosol in such conditions is beyond the scope of this paper. Thus, only fifteen children, out of some 400 patients of all ages who had been treated with penicillin aerosol, were considered relevant material for this analysis.

Tuberculosis and other serious illnesses being ruled out, the diagnosis of subacute or chronic bronchopulmonary infection was based on a history of recurrent respiratory episodes following measles pneumonia, whooping cough, tracheobronchitis, etc. The most characteristic symptom was persistent cough. The absence of abnormal clinical, roentgenologic, and laboratory findings was not considered as ruling out the diagnosis of bronchopulmonary infection. Bronchographic studies were done in eight patients with severe infection, in whom bronchiectasis seemed most likely.

The three following case reports and the tabulation of the fifteen cases (Table III) may demonstrate the various problems involved in children suffering from bronchopulmonary infection. They also may reveal the potentialities as well as the limitations of penicillin aerosol as a therapy.

CASE REPORTS

CASE 1.—The patient was an 11-year-old boy, first seen April 8, 1946. The mother suffered from bronchiectasis. The child previously was in good health except for minor respiratory episodes. He had had measles three months prior to examination, followed by persistent fever and cough. Sulfadiazine was given for four days, the symptoms subsided,

and the child was considered recovered after two more weeks. However, a productive cough continued. Physical and roentgenologic examination revealed unresolved bronchopneumonia in the left lower base. Penicillin aerosol therapy was administered for two months. The respiratory symptoms cleared up in ten days; the clinical and roentgenologic signs disappeared after one month. Treatment was continued for one more month. The patient remained in perfect health for eleven months after termination of treatment. In June, 1947, a mild productive cough reappeared without any abnormal clinical or roentgenologic findings. A second course of penicillin was given for three weeks with prompt response; there has been no recurrence of respiratory symptoms since then. The last check was on Jan. 15, 1948.

CASE 2—The patient was an 8 year old girl, first seen Oct. 18, 1945. There was no history of chronic respiratory diseases in the family. The child had no respiratory infections up to the age of 4. At that time she contracted pertussis, followed by mild but persistent cough. During each winter there were two to three febrile exacerbations. In October, 1944, she had pneumonia, treated at home with sulfonamides. The child was absent from school for six weeks due to poor general health and continuous cough. The condition improved during the following summer, however, with the beginning of fall, symptoms became worse again and the child had to stay home for another three weeks. There were no abnormal clinical or roentgenologic findings at the time of examination, she was in good general condition. Eight weeks of penicillin aerosol therapy eliminated all symptoms. There has been no relapse now for more than two years; the child has remained in perfect health.

CASE 3—The patient was a 12 year old girl first seen April 6, 1946. The father suffered from chronic bronchitis. Since the age of 10 months, the child had been affected by recurrent febrile respiratory episodes of persistent character. She had measles and pneumonia when 16 months old, followed by relapsing bronchitis. Tonsillectomy was performed at the age of 4, followed by aggravation of the condition. During the same year, she had pertussis. Antrum puncture was performed because of increasing respiratory symptoms. There were many hospital admissions, during which the condition was variously diagnosed. At the age of 5, asthmatic symptoms developed, and, since hay fever appeared in the picture, the condition was considered to be bronchial asthma. Skin tests were essentially negative, but allergy to house dust and bacterial allergy were suspected. In spite of allergic management, the cough with purulent, at times blood streaked, sputum increased in severity. Tuberculosis had been ruled out by several examinations. After entering school, the child was often absent for a prolonged period. Essential findings were: poor general condition, marked dyspnea, even at rest; vital capacity 0.8 L; wheezy and sonorous râles throughout both lungs; fluoroscopy and x ray of chest essentially negative except for restricted motion of diaphragm with breathing and increased bronchovascular markings. Bronchographic studies did not reveal demonstrable bronchiectasis. The sputum was mucopurulent, negative for acid fast bacteria, cultures revealed the prevalence of hemolytic streptococcus and *Staphylococcus aureus*.

The course under penicillin aerosol treatment was as follows: remarkable improvement of symptoms during the first week, after two months of treatment, hardly any cough, but still some wheezy dyspnea, especially on exertion. The general condition also improved considerably, the child gained 12 pounds in this period. During the first year of treatment, two minor relapses occurred when penicillin aerosol was discontinued tentatively, but they were controlled almost immediately by resumption of the treatment. At the end of the first year the condition seemed to be stabilized, the child had gained 28 pounds; the vital capacity had increased to 1.5 L, the only remaining symptom was dyspnea, mostly on exertion, occasionally of asthmatic type. After the child had been in good health for several months without penicillin aerosol, a major relapse occurred in November, 1947, probably due to reinfection from her sister, who suffered from tonsillitis at that time. The relapse was characterized by high fever, asthmatic dyspnea, and severe cough with purulent, bloody sputum. Clinical and x ray findings revealed atelectasis of the right middle lobe. The

TABLE III. OBSERVATIONS ON FIFTEEN CHILDREN WITH SUBACUTE AND CHRONIC BRONCHOPNEUMONARY INFECTION, TREATED WITH PYCNOPLAN AEROSOL

CASE NO.	AGE AT ONSET OF ILLNESS	AGE AT START OF TREATMENT	DURATION OF ILLNESS	EXPOSURE TO ENVIRONMENTAL INFECTION	ORIGINAL AND CONSECUTIVE RESPIRATORY INFECTIONS	CONDITION AT START OF TREATMENT	PERIOD OF OBSERVATION	RESULTS OF TREATMENT
1	11½ yr.	12 yr.	3 mo.	Mother, bronchocystitis	<i>Mycoplasma pneumoniae</i>	Acutely ill; unresolved bronchopneumonia	18 mo.	Complete recovery after 2 mo. treatment; one mild relapse
2	1 yr.	4½ yr.	4 yr.	None	<i>Pertussis</i> at 4 yr.; pneumonia at 7 yr.	General health fair; no abnormal findings; persistent respiratory symptoms	2½ yr.	Complete disappearance of symptoms after 2 mo. treatment; no recurrence; in excellent health
3	5 yr.	5½ yr.	3 mo.	None	<i>Tracheobronchitis</i> following (?) measles; several relapses	Good general health; persistent respiratory symptoms	1 yr.	Prompt response to treatment of 2 mo. duration; no recurrence
4	5½ yr.	6 yr.	6 mo.	Mother, bronchocystitis	<i>Pertussis</i>	Good general health; persistent tracheobronchitis	16 mo.	Prompt response to treatment of 2 mo. duration; one mild relapse
5	6 mo.	1½ yr.	3 yr.	Father, chronic bronchitis; one sister, recurrent bronchitis	<i>Laryngotracheobronchitis</i> at 6 mo.; repeated relapses	Fair; localized bronchitis	1 yr.	Completely recovered after 2 mo. treatment; no recurrence
6	4 yr.	15 yr.	11 yr.	None	<i>Pertussis</i> at 4; repeated pneumonias	Severely ill; emaciated; extreme dyspnea	2 yr.	Greatly improved under several courses of treatment; gained 26 lb.; is working regularly; at times mild respiratory symptoms
7	5½ yr.	9 yr.	4 yr.	Father, recurrent bronchitis	<i>Pertussis</i> at 5	Good general condition, except persistent respiratory symptoms; no abnormal findings	15 mo.	Prompt response to treatment of 2 mo. duration; one mild relapse
8	2 yr.	7 yr.	5 yr.	None	<i>Laryngotracheobronchitis</i> at 2; measles at 6; several exacerbations	Good general condition; severe respiratory symptoms; emphysema	15 mo.	Greatly improved; mild relapses controlled by resumption of treatment

9	6 mo.	3½ yr.	3 yr.	Father, chronic bronchitis; bronchiectasis (?)	<i>Laryngotracheo- bronchitis</i> at 6 mo.; 3 times broncho- pneumonia	Good general condition; persistent respiratory symptoms; basal pathology left base; bronchopneumonia (?)	13 mo.	Prompt response to treat- ment of 2 mo. duration; one relapse after scarlet fever; basal pathology cleared up
10	6 mo.	11 yr.	10½ yr.	None	<i>Pertussis</i> at 6 mo.; measles pneumonia at 11 yr.	Unresolved measles, pneumonia; acutely ill; emaciated	20 mo.	Completely recovered after 5 mo. treatment; one mild relapse; now in excellent health; gained 22 lb.
11	1 yr.	12 yr.	11 yr.	Father, chronic bronchitis	<i>Laryngotracheo- bronchitis</i> at 1 yr.; <i>pertussis</i> at 5; measles, pneumonia at 7	Severely ill; emaciated; diffuse bronchitis; em- physema, pulm. fibrosis	1½ yr.	Good results; symptoms greatly reduced; gained 35 lb.; condition apt to recur if treatment discontinued
12	2 yr.	13 yr.	11 yr.	None	<i>Laryngotracheo- bronchitis</i> at 2; measles at 10; bronchopneumonia at 12	Poor general condition; severe respiratory symp- toms; emphysema mild pulm. fibrosis	2 yr.	Prompt response to treat- ment of 4 mo. duration; one severe and one mild relapse; now in good health; gained 23 lb.
13	2 yr.	11 yr.	9 yr.	None	<i>Pneumonia</i> at 2; measles at 5; pneu- monia (?) at 10	Poor general condition; diffuse bronchitis; em- physema	2½ yr.	Greatly improved after 6 mo. treatment; one mild relapse shortly afterward; symptoms apt to recur if treatment discontinued; general condition greatly improved; gained 20 lb.; vital capacity slightly re- duced
14	3 yr.	18 yr.	15 yr.	None	<i>Respiratory strep- tococcal infection</i> at 3; bronchopneu- monia; pneumonia (?) at 7 yr.	Very poor; pneumonia right middle lobe; em- physema	15 mo.	Greatly improved, gained 14 lb., symptoms apt to recur if treatment discontinued; vital capacity moderately reduced
15	3 yr.	15 yr.	12 yr.	Mother; chronic bronchitis	<i>Pertussis</i> at 3; many acute exacerbations	Seriously ill; extreme respiratory difficulties; pulmonary fibrosis	15 mo.	Moderately improved; sev- eral severe relapses if treatment discontinued; vital capacity moderately reduced

condition cleared up slowly under penicillin given parenterally and by aerosol, combined with postural drainage, aminophyllin, and the like. At the time of the last examination, Feb. 2, 1948, the child was in good health, the only remaining symptom being slight wheezy dyspnea on exertion.

As became evident from the cases here tabulated and from many more cases not included in this series, the early results of penicillin aerosol treatment were very favorable in almost all patients with bronchopulmonary infection. In patients with early infection, the respiratory symptoms usually subsided within a week. Clinical findings indicative of tracheobronchitis disappeared after one to two weeks' treatment; resolution of a subacute bronchopneumonic process took place in one to two months. With continued treatment, the accomplished improvement of both the respiratory infection and the general condition became more and more obvious. Continuous normal temperature, increasing appetite, and a feeling of well-being proved the beneficial systemic reactions resulting from this therapy. Exposure to inclement weather and to physical exercise no longer was followed by an aggravation of the condition. Banal respiratory infections such as coryza no longer "settled down" in the chest. If an associated bacterial infection of the upper respiratory system was present, it usually cleared up, too. Coexisting true allergic manifestations were not influenced by the antibiotic. However, it became obvious that hypersensitivity to known allergens rarely caused a severe, uncontrollable condition as long as the infection remained subdued. In children whose asthma appeared to be related to bronchial infection alone, the asthma disappeared together with the other respiratory symptoms whenever the bronchial infection could be eliminated.

In patients with more advanced infection, especially if pulmonary fibrosis and emphysema had developed, the therapeutic effect was less prompt and complete. Nevertheless, the accomplished improvement surpassed by far, even in these instances, the results of previous treatments. As long as penicillin aerosol therapy was continued, and in a number of cases for a prolonged period after its termination, the respiratory symptoms were at least greatly reduced and the general condition improved to a great extent. Gains in weight of 10 pounds within the first few weeks were not unusual. The school attendance of many of the children, who before had missed several weeks every year, became more regular again and frequently as normal as that of other children; exercises such as skating were much better tolerated.

However, the follow-up of the fifteen children clearly demonstrated that favorable early results do not always indicate the actual arrest of the infection, especially in children who had been severely ill for many years. It is difficult to say whether in a given patient the recurrence of bronchopulmonary infection was due to a new infection or whether a residual infection had become active again. It appears that the tendency to relapses was less pronounced in patients with early infection than in those whose illness was of long duration with preceding exacerbations and intervening respiratory infections. Moreover, the recurrence of respiratory symptoms whenever they appeared could, in mild cases, be easily controlled by a short consecutive course with penicillin aerosol,

whereas in patients with definitely chronic conditions, relapses frequently occurred as soon as penicillin aerosol was discontinued, and a more intensive treatment was then required. In these patients the response to the antibiotic was similar to that in patients with frank bronchiectasis, even if no bronchial dilatation could be demonstrated by lipiodol studies. As in bronchiectasis, the sputum never became free from pyogenic organisms, or the condition persisted to some extent, even in the absence of these bacteria.

SUMMARY

The prospects for prevention of chronic bronchitis and bronchiectasis largely depend on recognition and eradication of the initial bronchopulmonary infections at the earliest possible stage. Thus far, penicillin aerosol treatment seems the best available method for achieving the latter. It may be that more potent methods will be developed in the future. However, the most effective treatment cannot secure permanent cure, even in the mildest cases, if patients do not obtain the same attention after their recovery as given to patients with other fundamentally chronic diseases. The follow-up method used in rheumatic fever, tuberculosis, and the like should be applied also to children with potential bronchiectasis, in order to give undelayed treatment in the case of a relapse before it adds new damage to the respiratory system.

The prognosis for arrest of definitely chronic cases by penicillin aerosol therapy alone is less favorable. Nevertheless, encouraging results have been obtained by this new method, even in children with pulmonary fibrosis and emphysema. Therefore, the hope seems to be justified that penicillin aerosol treatment, combined with other methods such as bronchoscopic aspiration of bronchial secretion and systematic postural drainage, may eventually lead to the arrest of the condition. Such therapeutic measures against the local disease must be supplemented by measures directed toward improvement of the general health. As in tuberculosis, a prolonged convalescence in healthful surroundings appears essential in all but the mildest cases.

Most of all, it should be realized that this common and apparently communicable infection is a public health problem. It is true that the condition has less spectacular features than certain other diseases which, although less common, attract wider attention. However, its often serious character and the great economic burden upon the individual and the community should be sufficient reasons for recognizing that here, too, possible prevention is a sounder approach than belated curative efforts. Since the disease is prevalent in poor families, chest clinics and public convalescence homes for nontuberculous pulmonary disease are needed. Finally, public enlightenment about prophylactic measures and greater knowledge among the coming generation of physicians will give a strong impulse to individual efforts in the prevention of chronic bronchitis and bronchiectasis.

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EARLY WHOOPING COUGH IMMUNIZATION

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THIS paper relates our experiences with whooping cough immunization in infants under 6 months of age, using alum-precipitated vaccine. The purpose of the investigation is threefold: first, to determine if Sako's¹ work on early whooping cough immunization could be repeated; second, to correlate the Flosdorf² skin test with the rapid slide agglutination test; third, to observe the incidence of local and systemic reactions.

MATERIALS AND METHODS

Since 1946 the city of Dallas has been furnished whooping cough vaccine by the Texas State Laboratory. The vaccine is phase I of *Hemophilus pertussis*, alum-precipitated, and standardized to contain 40 billion organisms per cubic centimeter. The infants in this study were white, Negro, and Mexican who attended the City Well-Child Conferences. They were immunized with 0.2 c.c., 0.3 c.c., and 0.5 c.c. of this vaccine at four-week intervals for a total of 1.0 c.c. Some infants in this series received their first injection at 2 weeks of age. The greatest number began their immunization at one month of age, which was usually the time of their first visit.

The agglutination test* was performed by the rapid slide method of Powell and Jamieson.³ The procedure followed was exactly as described by them. Care was taken not to rock the card more than one minute. In forty infants the antigen used was first centrifuged, the supernatant fluid poured off, and the antigen resuspended in albumin. No difference was noted in the results with the albumin-suspended antigen when compared with the usual antigen.

The skin test† of Flosdorf was performed by injecting 0.1 c.c. of the agglutinin intracutaneously into the forearm. The area of induration was measured at the end of twenty-four hours. An area of 10 mm. or more was considered an immune or positive reaction. All tests were performed by us.

The first 117 infants receiving skin and agglutination tests prior to the first injection of whooping cough vaccine served as controls. All infants had the skin and agglutination tests performed three to four months after the last whooping cough injection. A form was devised which had the child's name, address, age, sex, date of injection, type of reactions, and results of tests. The reactions looked for were fever, induration, and abscess. The mothers were questioned about fever. This was quite unreliable since very few mothers used a thermometer. The presence of induration and abscess was noted by us. The

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*The material for this test was furnished by Eli Lilly & Company, Indianapolis.

†In this test the agglutinin was supplied by Sharp & Dohme, Inc., Philadelphia.

vaccine was given by the City Health Nurses, who were instructed as follows: (1) Use a clean dry needle; (2) inject deeply and distally into the deltoid; (3) use a small amount of air to clear the needle.

RESULTS

Table I reports the results of the skin and agglutination tests in 117 infants before their first injection of whooping cough vaccine. None of the infants in the group showed a positive skin test. Sixteen had positive agglutination tests. Mothers of the infants with positive agglutination tests were also tested and showed similar results. However, a number of mothers with positive agglutination tests had infants who showed negative agglutination tests.

The infants were divided into two groups, A and B. In Group A, immunization was completed before the end of the fourth month. In Group B, it was completed between the fourth and sixth months. (See Tables II and III.)

In Group A there were twenty-two infants who received their first injection at 2 weeks, and their immunization was completed at 10 weeks. All of these responded well as judged by these tests. The infants with negative skin reactions had positive serum agglutinations, and those with negative agglutination tests had positive or immune skin reactions. Thus no infant in the entire series had both a negative skin reaction and a negative serum agglutination.

TABLE I. INFANTS TESTED BEFORE WHOOPING COUGH VACCINE WAS ADMINISTERED

AGGLUTINATION TEST			SKIN TEST	
NEGATIVE	WEAKLY POSITIVE	STRONGLY POSITIVE	NEGATIVE	POSITIVE
101	13	3	115	2 (doubtful)

TABLE II. INFANTS IN WHOM IMMUNIZATION WAS COMPLETED BEFORE THE AGE OF 4 MONTHS (GROUP A)

AGGLUTINATION TEST			SKIN TEST	
NEGATIVE	WEAKLY POSITIVE	STRONGLY POSITIVE	NEGATIVE	POSITIVE
10	37	68	3	112

TABLE III. INFANTS IN WHOM IMMUNIZATION WAS COMPLETED BETWEEN THE AGES OF 4 AND 6 MONTHS (GROUP B)

AGGLUTINATION TEST			SKIN TEST	
NEGATIVE	WEAKLY POSITIVE	STRONGLY POSITIVE	NEGATIVE	POSITIVE
1	14	45	4	56

TABLE IV. INCIDENCE OF REACTIONS IN GROUP A

NUMBER OBSERVED	NO REACTION	FEVER	INDURATION	FEVER AND INDURATION	ABSCESS
106	75	4	11	13	3

TABLE V. INCIDENCE OF REACTIONS IN GROUP B

NUMBER OBSERVED	NO REACTION	FEVER	INDURATION	FEVER AND INDURATION	ABSCESS
55	35	3	8	9	0

It should be noted that the induration usually was small and that often the mother was completely unaware of it. Fever was rarely high or of long duration. In the three children with abscess formation the process cleared spontaneously and apparently did not affect the infants. During the two years of this study none of the infants in this series was reported to us as having developed whooping cough.

DISCUSSION

Sako and his associates,⁴ and later Sako¹ alone, immunized a very large series of infants under 3 months of age with alum-precipitated whooping cough vaccine. They demonstrated conclusively that this was an effective immunologic procedure as judged by clinical and serologic results. Waddell and L'Engle,⁵ using a fluid vaccine with a total dose of 100 billion organisms, inoculated 129 infants beginning at the age of one week, and observed that many responded with a very satisfactory titer. Recently Adams, Kimball, and Adams⁶ noted in a small series of infants under 3 months of age that fluid vaccine produced a rise in antibody titer in many of them.

In the series of Sako and his associates,⁴ the incidence of whooping cough was greater in the group of infants immunized before the age of 6 months than in the older group. However, there were no deaths, and the disease was milder in the immunized group when compared with unvaccinated infants. On the basis of these studies, Sako and later Waddell and L'Engle recommend that whooping cough vaccine injections be instituted at one month of age.

Lapin⁷ stated that whooping cough vaccine was without value in young infants. He said that "Theoretical analogy with other immunizations and Sauer's discouraging results under 6 months more than counterbalance the recent report of Sako and his associates." It should be pointed out that while in 1941 Sauer⁸ reported he could not protect young infants as successfully as he did those over 7 months, he had no deaths and the disease was milder in the immunized group. Sauer⁸ now believes that with the use of alum-precipitated vaccine he can obtain results in young infants that are quite comparable to those over 7 months.

This investigation was planned to conform with the studies of Sako and his associates.⁴ We repeated his work, using the same type of vaccine with an identical dosage schedule and the same age group of infants. Our results in this much smaller group as judged by serologic and skin tests are very similar to Sako's. The incidence of reactions is about the same. Fever is scarcely ever observed; however, in private practice fluid vaccine leads to many more febrile reactions. Induration is only slight and often overlooked by the mother. Abscess formation is not distressing; however, it is a cause of anxiety in the mothers. It appeared in one white infant and two Negro infants in our series and in each case the abscess healed spontaneously. We believe it can largely be avoided by the use of a dry needle, injecting deeply and distally into the upper arm, and following with 0.1 c.c. of air to clear the needle.

It seems that the procedure of using alum-precipitated vaccine, standardized to contain 40 billion organisms per cubic centimeter and given in doses of 0.2 c.c.,

0.3 c.c., and 0.5 c.c. at monthly intervals to infants at one month of age is very effective. Moreover, it appears to be the most valuable method available at present for reducing the mortality and morbidity rate in infants under 6 months of age.

It is not the purpose of this paper to enter into a lengthy discussion of the value and reliability of the agglutination and skin tests. Suffice it to say that the establishment of the clinical effectiveness of a pertussis vaccine, as has been pointed out by numerous students of this problem, is extremely difficult. Comparable groups of vaccinated and nonvaccinated children are almost impossible to obtain. Moreover, the severity of the disease varies from year to year and with different localities. In addition, it is quite conceivable that *Bacillus parapertussis* may account for some cases of so-called whooping cough.

For these reasons most investigators have resorted to various laboratory tests to determine the effectiveness of pertussis vaccine. The mouse protection test,¹⁰ the agglutination test,^{3, 11} the complement fixation test,⁹ the opsonocytaphagic test,¹²⁻¹⁴ and the skin test of Flosdorf^{15, 16, 20} have all been used as a measure of the efficacy of pertussis vaccine. Lapin¹⁷ has summarized the pros and cons of the various tests. When more than one test has been done, a fair degree of correlation has been noted.¹⁹⁻²² It appears that these different tests measure various aspects of the same immunologic process.

In the present study the agglutination tests were made by the rapid slide method of Powell and Jamieson.³ This test has been correlated with the quantitative test by Sako and his associates.^{1, 4} They found that a moderately positive and a strongly positive rapid agglutination test indicated a titer of 1:160 or more. Sako, in a personal communication, stated that if the rapid slide agglutination method is done correctly and the individual develops experience with it, the test is a reliable one. DeGara and Mayer²³ correlated the slide agglutination test with the quantitative method. When one studies their results it is apparent that the slide method errs on the low side, that is to say it will be negative when the tube method is negative or shows a low titer. When the slide method is strongly positive the titer is always high. It is only with the weakly positive slide agglutination that one may miss some of the higher titers. Mishnlow²⁶ observed a close relationship between the two methods.

Miller and his associates¹⁸ and later Sako¹ demonstrated that clinical immunity corresponded to the agglutination titer. No children with a titer of 1:320 or more developed whooping cough. However, there were those with a negative agglutination test who did not take whooping cough after exposure. Felton and Flosdorf²⁴ felt that the children who were protected in the absence of circulating antibodies had cellular antibodies present as measured by a positive skin test.

The Flosdorf skin test appears to be a reliable method for detecting susceptibles and the effectiveness of whooping cough vaccine. Felton and Flosdorf²⁴ and Felton and his associates²⁵ have observed a close correlation between the agglutininogen skin test and the clinical and agglutination methods. Sauer and Markley²⁰ compared the skin test with the complement fixation reaction and observed a good correlation between them.

Reference to Table I shows that there were sixteen infants with demonstrable humoral antibodies before the first injection of whooping cough vaccine. The passage of maternal antibodies of whooping cough has been observed by others. The skin tests were negative in all but two infants, and in them it was doubtful. This is in agreement with Felton and Flosdorf,²⁴ who never found a positive skin test in young nonimmunized infants. Apparently the passage of antibodies in the infants has no effect upon cellular antibody formation.

Tables II and III demonstrate that there is a high degree of correlation between the rapid slide method and the skin test. We do not have a satisfactory explanation for the fact that a few infants had positive agglutination tests with negative skin reactions. This might be due to the fact that the area of induration, although less than 10 mm., signified immunity. Perhaps some of these children would have shown a delayed positive reaction if observed on the fifth day. Sauer and Markley²⁰ have observed infants with humoral antibodies as measured by the complement fixation test who had negative skin reactions.

We agree with Tucker²⁷ that the agglutinin skin test is simple, reliable, and specific. Perhaps 10 mm. is too large an area of induration to differentiate the immune from the susceptibles. Were this true, it would explain the negative skin reaction in the infants with positive agglutination tests. It may be that any area of induration is significant. We are now investigating this point.

SUMMARY

Whooping cough immunization with an alum-precipitated vaccine containing 40 billion organisms per cubic centimeter given in doses of 0.2 c.c., 0.3 c.c. and 0.5 c.c. at monthly intervals was used in infants of one month of age or less. It proved to be an effective immunologic procedure as judged by clinical, serologic, and skin tests. Reactions were minimal and abscesses uncommon. If the proper technique is used in administering the vaccine, abscess can perhaps be eliminated. The agglutinin skin test and the rapid slide agglutination method showed a high degree of correlation. The skin test is a simple, reliable, and effective method for determining immunity following pertussis immunization.

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HEART DISEASE IN SAN FRANCISCO SCHOOL CHILDREN

1947 REGISTRY SHOWING INCIDENCE, PROBLEMS, AND SUPERVISION TECHNIQUES

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RECOGNITION of the need for a close check on rheumatic fever as on tuberculosis has led San Francisco to pioneer in the establishment of a central registry of cardiac children in its schools. The question of the incidence of heart disease, particularly of rheumatic fever and rheumatic heart disease, has been an unanswered one in this area for many years. The central registry was devised, therefore, to serve a double purpose: case finding, and follow-up. This registry was started at the beginning of the school term in September, 1946. By the end of the June, 1947 term there were 1,120 children with heart disease known to the registry. In this registry we have attempted to include as much vital information as possible regarding each child. Our sources of information were many:

1. School nurses submitted lists of all children in their schools known to have cardiac disease. These lists were compiled from reports of school physicians and private physicians and clinics caring for the children.

2. Physicians reported new cases of rheumatic fever. This is required by law in California.

3. Many children had their cardiac status clarified by examinations in 100 of the 153 schools served by the San Francisco Department of Public Health; a study to be subsequently described.

4. The files of the School Diagnostic Center of the San Francisco Department of Public Health revealed many of the cases.

5. A major source of information regarding active cases of rheumatic fever proved to be the requests for home teachers for the children.

6. Reports to the Crippled Children's Services of the San Francisco Department of Public Health supplemented other sources.

There have been previous surveys of this problem in San Francisco. One by Ina Richter⁸ in 1931 included children examined at the School Diagnostic Center of the San Francisco Department of Public Health during the years 1929 to 1931. A second study in 1937 by Sampson and his associates¹⁰ included not only the cases examined at the School Diagnostic Center but a survey of 295 children examined in the schools by Dr. John Sampson. We shall indicate the similarity between our studies and those of the previous workers, particularly the one completed ten years ago.

It is to be emphasized that this registry is a current one—i.e., it includes only those children about whose cardiac status definite information was received

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TABLE I. RHEUMATIC CHILDREN KNOWN TO CENTRAL CARDIAC REGISTRY SEPTEMBER, 1946, TO JUNE, 1947

DIAGNOSIS	BOYS		GIRLS		PRE-SCHOOL	TOTAL
	5-10 YRS.	10-18 YRS.	5-10 YRS.	10-18 YRS.		
Active rheumatic fever	33	46	30	77	11	197
Known recurrent rheumatic fever		3	8	17		28
Questionable rheumatic fever	4	3	7	6		20
Rheumatic heart disease	18	86	13	82(1 SBE)		199
Potential rheumatic heart disease	42	91	25	75	1	234
Rheumatic and congenital		6	1	1(active)		8
Rheumatic vs. congenital	4	4	2	5		15
Rheumatic vs. functional	5	19	2	21		47
Totals	106	258	88	284	12	748

TABLE II. CHILDREN WITH CONGENITAL HEART DISEASE IN CENTRAL CARDIAC REGISTRY, SEPTEMBER, 1946, TO JUNE, 1947

DIAGNOSIS	BOYS		GIRLS		PRE-SCHOOL	TOTAL
	5-10 YRS.	10-18 YRS.	5-10 YRS.	10-18 YRS.		
I.V. septal defect	16	24	16	25		81
I.A. septal defect	11	2	6			19
Patent ductus	2	4	6	6	1	19
Other types	20	22	16	14	2	74
Congenital vs. functional	6	16	6	14	5	47
Totals	55	68	50	59	8	240
<i>Other Diagnoses</i>						
Organic vs. functional	22	33	16	16	2	89
Being followed to complete diagnosis	3	14	6	13		36
Miscellaneous		4		3		7
Totals	25	51	22	32	2	132
Grand Total Cardiac Children in Registry to Date (Tables I and II)						1,120

during the school year of September, 1946, to June, 1947. A summary of this registry is shown in Tables I and II.

Table I: Rheumatic Children Known to Central Cardiac Registry, September, 1946 to June, 1947.—It can be seen that there were 225 children with active rheumatic fever, of which only twenty-eight were known to have recurrent cases. If we include those in whom the diagnosis was in doubt, there was a total of 245 children with active rheumatic fever during the nine months represented. (Eleven of these children were of preschool age.) This does not include children admitted to San Francisco hospitals from other parts of the state.

In addition there were 199 children with inactive rheumatic heart disease but with classical signs of rheumatic valvulitis. It is to be emphasized that we were very conservative in our diagnoses. Those with signs which were at all questionable were placed in other categories.

There were 234 children with potential rheumatic heart disease, further defined by us as children known to have had rheumatic fever within the past ten years but at this time showing no characteristic evidence of heart disease. There were eight cases which we believe represented rheumatic heart disease superimposed upon a known congenital lesion, usually an interauricular septal defect.

The remainder were those doubtful patients previously mentioned in whom we could not make a more accurate diagnosis at that time.

Table II: Children With Congenital Heart Disease in Central Cardiac Registry, September, 1946 to June, 1947.—There were 240 children with congenital cardiac defects. This group was almost as large as the group with active rheumatic fever. The most common lesion was the patent interventricular septal defect, of which there were eighty-one. There were nineteen children with interauricular septal defects, and the same number with a patent ductus arteriosus. The remainder, including children with the cyanotic types and such diagnoses as subaortic stenosis and coarctation of the aorta, are grouped together under one heading but are rapidly being classified as information is obtained. There were forty-seven children in whom the findings were such that a definite differentiation between a congenital lesion and a nonorganic functional murmur was not made at the time. All of the latter will be followed at regular intervals.

Thus the total number of children known to have either actual or potential heart disease totals 1,120. We are convinced, however, that this represents an absolute minimum in all categories.

We feel that the great value of the registry is that it shows more than mere figures. It includes the essential personal history of each child, including the type of medical supervision, hospital admissions, convalescent care, follow-up reports, and any other information which will aid in determining the current cardiac status of each child, and ultimately, to the better integration of his total care. In this respect we have followed the London County Council's Rheumatic Scheme, first organized in 1926.

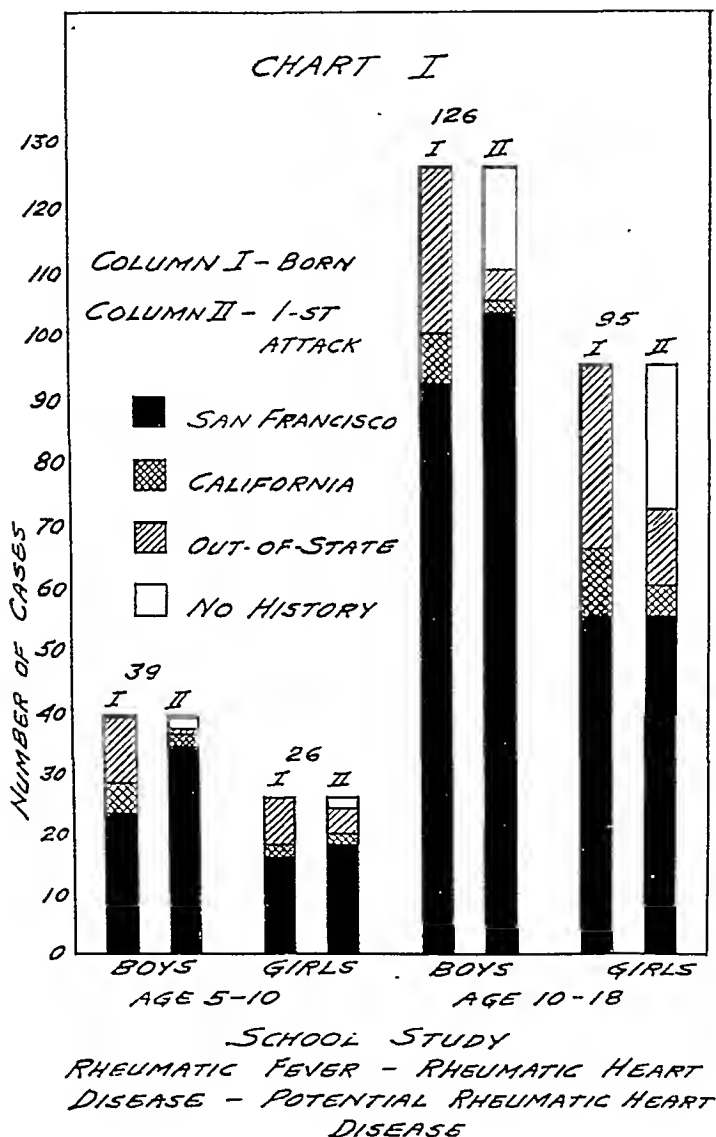
SCHOOL STUDY: SURVEY OF HEART DISEASE IN 100 SAN FRANCISCO SCHOOLS

The following is the report of a survey of cardiac disease made in 100 San Francisco schools, including elementary, junior high, and high schools, both public and parochial. The population of the schools which we visited was approximately 57,768, more than half of all children attending San Francisco schools. We examined only those children who had previously been selected by either school physician, private physician, or clinic, and some suspects chosen by the school nurse from history and observation. In other words, we examined only those children already suspected to have cardiac disease.

Altogether in the school check we examined 698 children between the ages of 5 and 18 years. These children were examined in their own schools or in nearby health centers during the school year of September, 1946, to June, 1947. During the first term one of us (S. J. R.) made all of the examinations; during the second semester another worker joined the project (D. M. A.). The chief purpose in performing these examinations was to determine the current status of children listed by the school nurses as having a history of cardiac disease or rheumatic fever as reported to them in turn by a private physician, clinic, or the school physician. Thus we planned to examine only known cardiac suspects. That we found nine children with active rheumatic fever attending school was an accidental, if important, product of our work. We were also interested in

determining the medical supervision of these children. Although all of them were presumed to have cardiac disease, 17.4 per cent of them were found to have no medical supervision of any kind.

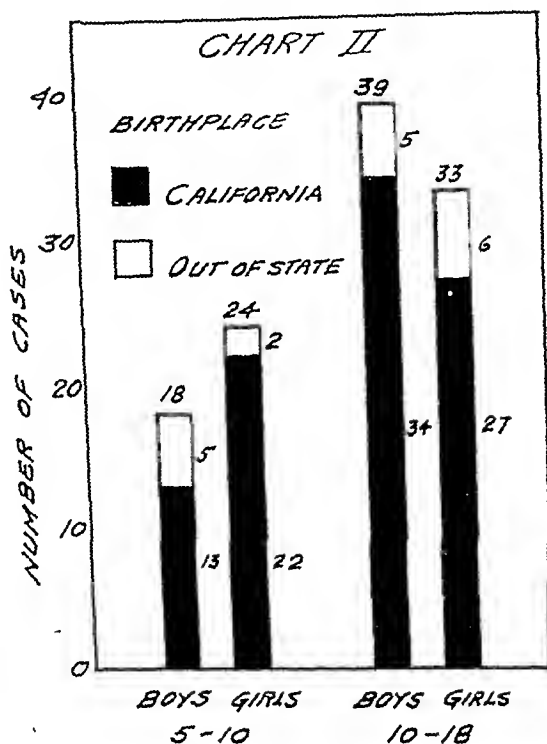
Table III: School Survey.—It can be seen that of the 199 children known to the cardiac registry as having rheumatic heart disease, 111 were examined in



school by the authors. The nine children with active rheumatic fever were found accidentally. While we were at the school an astute nurse would ask us to examine a child with suspicious symptoms, chiefly fatigue or pallor. These

children were immediately referred to proper medical supervision and were subsequently hospitalized, put to bed at home, or sent to convalescent institutions. Each of them was proved to have acute or subacute rheumatic fever.

The children with congenital lesions plus rheumatic heart disease have been previously mentioned. There were nine of these. There were 171 children with a history of rheumatic fever in whom we could find no definite evidence of cardiac involvement at this time. These children we classified as having potential rheumatic heart disease.



*SCHOOL STUDY
CONGENITAL HEART DISEASE*

Table IV: School Study.—There were 114 children with congenital lesions, of whom thirteen would be considered operable at the present time. Some of these have since undergone operation. The remaining children represent miscellaneous or doubtful cases. As in other surveys, we found 195 children in whom there was no evidence or history of cardiac disease although they had been considered cardiac suspects. They included children with murmurs which we did not consider to represent cardiac disease—i.e., functional heart murmurs.

Tables V and VI show the comparison of our findings with those of Sampson and his associates in 1937. Although his examinations represented a smaller number of the school population, it can be seen that there is no marked difference

TABLE III. SUMMARY OF RESULTS OF EXAMINATIONS IN 100 SAN FRANCISCO SCHOOLS^{*}

RHEUMATIC HEART DISEASE		NO. OF CHILDREN
Children with rheumatic heart disease		111
Children with active rheumatic fever attending school		9
Children with rheumatic plus congenital heart disease (Children who have signs of congenital heart disease and in addition, have a history and signs which are indicative of superimposed rheumatic heart disease.)		9
Children with potential rheumatic heart disease (Children with a definite history of rheumatic fever within the last ten years but who have no evidence of cardiac involvement at this time.)		171
Rheumatic vs. congenital (Children with organic heart disease not differentiated by means at our disposal at time of examination.)		12
Rheumatic vs. functional (Children with no history of rheumatic fever but with signs which were suspicious of cardiac involvement.)		23
Total		335
*School population represented		57,768
Total children examined		698
Per cent of population examined		1.2

TABLE IV. SUMMARY OF RESULTS OF EXAMINATIONS IN 100 SAN FRANCISCO SCHOOLS

CONGENITAL HEART DISEASE		NO. OF CHILDREN
Interauricular septal defects		26
Interventricular septal defects		61
Other defects		27
Patent ductus arteriosus		9
Tetralogy of Fallot		3
Coarctation of aorta		1
Unspecified		14
Congenital vs. functional (Children in whom at the time of examination no differentiation could be made between nonorganic signs and those indicative of a congenital heart lesion.)		19
Organic vs. functional (Children with no history but with signs which could not be differentiated, i.e., as between functional heart murmur, rheumatic or congenital heart disease.)		26
Miscellaneous (2 hypertension, 1 thyrotoxic heart disease, 1 sickle cell anemia, 1 erythroblastic anemia, 1 gonorrheal (arthritis).)		6
Undetermined Children with no evidence nor history of cardiac disease although labeled as cardiac suspects (functional murmur)		3 195
Total		363

TABLE V. INCIDENCE OF CONGENITAL AND RHEUMATIC HEART DISEASE IN 197 CARDIAC SUSPECTS FOUND AMONG 13,338 SCHOOL CHILDREN IN 1937*

SCHOOL POPULATION REPRESENTED	HEART DISEASE SUSPECTS	ORGANIC HEART DISEASE	RHEUMATIC		CONGENITAL		RATES PER 1,000 SCHOOL POPULATION		
			TOTAL	%	TOTAL	%	ORGANIC	RHEUMATIC	CONGENITAL
1,338	197	49	30	62	19	38	3.7	2.2	1.4

*Sampson, Christie, and Gelger¹⁰

in the final results. Sampson found that 62 per cent of his cases of total organic heart disease represented rheumatic involvement, while we found the figure to be 55.3 per cent. We found a higher percentage of congenital lesions, 44.7 per

cent as compared with 38 per cent by Sampson. As will be seen in Table VII, this percentage difference between rheumatic and congenital heart disease is almost identical with that found by Rauh² in Cincinnati schools in 1938. We would like to emphasize that the rheumatic children we examined were of necessity in the inactive phase. The incidence of 4.4 per 1,000 does not include the 245 children with active rheumatic fever, many of whom will undoubtedly develop a valvulitis.

TABLE VI. INCIDENCE OF CONGENITAL AND RHEUMATIC HEART DISEASE IN 698 CARDIAC SUSPECTS FOUND AMONG 57,768 SCHOOL CHILDREN IN 1947*

SCHOOL POPULATION REPRE- SENTED	HEART DISEASE SUSPECTS	ORGANIC HEART DISEASE	RHEUMATIC		CONGENITAL		RATES PER 1,000 SCHOOL POPULATION		
			TOTAL	%	TOTAL	%	ORGANIC	RHEUMATIC	CONGENITAL
57,768	698	255	141	55.3	114	44.7	4.4	2.43	1.9

*Robinson, Aggeler, and Daniloff, September, 1946 to June, 1947.

In summary, we found that 4.4 children per 1,000 school population had organic heart disease, of which 2.43 per 1,000 had rheumatic heart disease (inactive) and 1.9 per 1,000 had congenital heart disease. To interpose Dr. Ina Richter's⁵ figures of 1929-1931, she examined 319 children with organic heart disease at the School Diagnostic Center, of whom 151, or 47 per cent, had rheumatic heart disease, and 140, or 44 per cent, had congenital heart disease.

Table VII shows the incidence of heart disease in school children in other cities. A direct comparison is not accurate because of the various age groups and types of examinations performed. However, it can be seen that those studies which assumed that 80 per cent of organic heart disease was rheumatic in origin may well be subject to some revision. In a late study in Washington County, Iowa, which involved a small number of school children, Jackson⁴ found that 58 per cent had rheumatic heart disease and 42 per cent had congenital heart disease.

RHEUMATIC FEVER INDIGENOUS TO CALIFORNIA

In the school study we also tried to ascertain where the children acquired the rheumatic fever. There has been a consistent tendency to state that most cases of rheumatic fever and rheumatic heart disease in California were the result of the migration from the East and Middle West. Dr. Helen Johnson,¹¹ in a study covering five years in Contra Costa and Solano Counties, California, found that 81.4 per cent of all children with rheumatic heart disease, when the history of rheumatic fever could be obtained, had their first attack in California.

Chart I shows that 286 children in the school study had either a history of rheumatic fever or evidence of rheumatic heart disease. The number born out of state was seventy-four, but of these, only twenty-two had their known initial attack of rheumatic fever out of the state, which gives an incidence of 80 per cent who had their first attack of rheumatic fever in California. Davis and Rosin¹ studied the hospital admissions to Los Angeles County Hospital for rheumatic fever between the years 1936 and 1941. There were 157 patients with

TABLE VII. INCIDENCE OF HEART DISEASE IN SCHOOL POPULATIONS OF CITIES IN THE UNITED STATES

CITY	NUMBER OF SCHOOL CHILDREN REP- RESENTED	NUMBER EXAM- INED IN SURVEY	AGE	SEX	ORGANIC HEART DISEASE PER 1,000	RHEU- MATIC HEART DISEASE PER 1,000	CONGENI- TAL HEART DISEASE PER 1,000
San Francisco (Author Survey, 1946- 1947)	57,678	698	5-18	M. & F.	4.4	2.43	1.9
San Francisco ¹⁰ (1937)	13,338	197	5-19	M. & F.	3.7	2.2	1.4
Denver ¹² (1945)	1,051	114	12-19	M. & F.		4.8	
Eureka, Calif. ¹¹ (1939- 1941)	2,450	2,450	5-19	M. & F.	20.7	20.0	0.7
Denver ¹² (1945)	1,845	1,845	12-19	F	19.0	16.3	2.7
Redlands, Calif. ¹¹ (1939-1941)	2,635	2,635	5-19	M. & F.	4.6	3.8	0.8
Susanville, Calif. ¹¹ (1939-1941)	732	732	5-19	M. & F.	1.5	1.1	0.4
Cincinnati ¹¹ (1927)	6,960				3.7		
Cincinnati ⁷ (1938)	85,389	1,782	5-19	M. & F.	3.6	2.0	1.6
Philadelphia ² (1937)	33,293	863	6-18	M. & F.	5.9	5.0	0.9
Louisville, Ky. ¹³ (1941)	41,905		6-15	M. & F.	5.2	3.6	1.6
Boston ⁹ (1927)	119,337	2,311	6-15	M. & F.	5.0	4.5	0.5
Washington Co., Iowa ⁴ (1945)	5,058	5,058	5-19	M. & F.	4.7	2.72	1.98

this diagnosis admitted to the Pediatric Department during this period. Of these, 103, or 65.7 per cent, were born and reared in Los Angeles. Of the fifty-four children born out of the city, forty-two had lived in Los Angeles for at least one year prior to the first attack. While we did not explore the familial incidence of rheumatic fever in those children born out of the state, we were impressed by the fact that those children born out of San Francisco came here to have their rheumatic fever.

Chart II shows the place of birth of children with congenital heart disease, which was also of interest to us. Of 114 children with congenital heart disease, ninety-six, or 85.1 per cent, were born in California, while only seventeen, or 14.9 per cent, were born out of the state. This finding refutes an oft-repeated statement that families with children who have congenital cardiac defects seek the milder climate of California.

While we divided the children by age groups, 5 to 10, and 10 to 18, and by sex also, we did not consider the results of sufficient significance to do more than note them, as can be seen in the tables and charts.

In conclusion, it may be stated that as of June, 1947:

1. There were over 1,000 cases of heart disease in children of school age in San Francisco known to an operating cardiac registry.
2. There were 234 cases of active rheumatic fever among the children 5 to 18 years of age and eleven cases in children of preschool age, a total of 245.
3. Out of every 1,000 school children, 2.43 had rheumatic heart disease—i.e., valvulitis. (This does not include 245 active cases.)
4. Almost 2 (1.9) out of every 1,000 had some type of congenital heart disease.

5. Eight-five per cent of the children with cardiac disease were born in San Francisco or somewhere in California, and were reared here.

6. The problem of preventable heart disease is a significant one in San Francisco, and measures for its prevention and control remain a major medical problem.

PURPOSE OF REGISTRY

Since June, 1947, when 1,120 children were known to the central cardiac registry, a considerable number of children have been added. The figure changes every day. Many of the children counted in the June, 1947, figure as having potential rheumatic heart disease have had recurrences of rheumatic fever. New cases have been found. We want to stress the fact that this registry is not just a pack of cards. It provides a method of following these children through the years to be sure that they stay under medical supervision, that they may have hospital and other institutional care when indicated, that the circumstances of their lives may be eased when necessary, that they may have the proper education for their physical limitations, and that they may be protected in every way possible from the recurrent infections that are so dangerous to them.

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FURTHER EXPERIENCE WITH THE HYPOXIA TOLERANCE TEST OF THE HEART IN CHILDREN

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THE preliminary report on the hypoxia tolerance test of the heart in children was published in 1946.¹⁴ The normal cases as well as those with pathologic findings were few, but the results were so encouraging that further studies were made. Today our experience is greater; we have at this time examined 365 patients and taken about 600 tests. Since we have not been able to examine all cardiac patients in our clinic we have chosen special groups in accordance with our research plans during the last years.

The test is performed with a special apparatus previously described.¹⁴ As a rule the children were given 9 per cent oxygen for a period of ten minutes. The effect of the test was measured by means of electrocardiography and phonocardiography, and in a few cases the arterial oxygen saturation was followed by means of an oximeter.

The age distribution of the cases is illustrated in Fig. 1.

Fig. 2 gives data regarding the cases in the normal group and those in the group with subjective symptoms but no clinical signs. As the latter group, in our opinion, does not contain any cases of real cardiac disease, both groups together could be looked upon as our normal material. In only two cases out of ninety-three have there been positive reactions.

Fig. 2 also shows forty-two cases of rheumatic heart disease, sixty-four cases of active and healed myocarditis, and forty-four cases of gallop rhythm, and represents the result of the tests made in acquired heart disease. In active rheumatic carditis about three-quarters of the cases have been positive. About 75 per cent of the patients with healed lesions (with or without a rheumatic valve disease) have reacted negatively. It is perhaps astonishing that there is such a high percentage of negative cases in this group, but it contains remarkably few cases of a more severe nature. On the whole it would seem that rheumatic heart disease in Sweden today is much rarer and milder than it was in previous years. The myocarditis group is not quite uniform. We have tried in this group to collect cases with clinical electrocardiographic or roentgenologic findings. The result has been about the same as for the rheumatic group. Thus, about 75 per cent of cases of active myocarditis (rheumatic cases of course excluded) have shown a positive result. The corresponding figure for patients with healed lesions is only 20.5 per cent. Out of forty-four patients with gallop rhythm without other signs of cardiac disease, more than one quarter (27.3 per cent) have given a positive reaction to the hypoxia test. This result, together with the result in the healed myocarditis group, speaks in favor of the opinion, empha-

From the Pediatric Clinic of the Crown Princess Lovisa's Children's Hospital in Stockholm.

Aided by grants from Therese and Johan Anderson Memorial Fund and from the Swedish Medical Research Council.

Hypoxia tolerance test

Age and sex distribution

365 cases

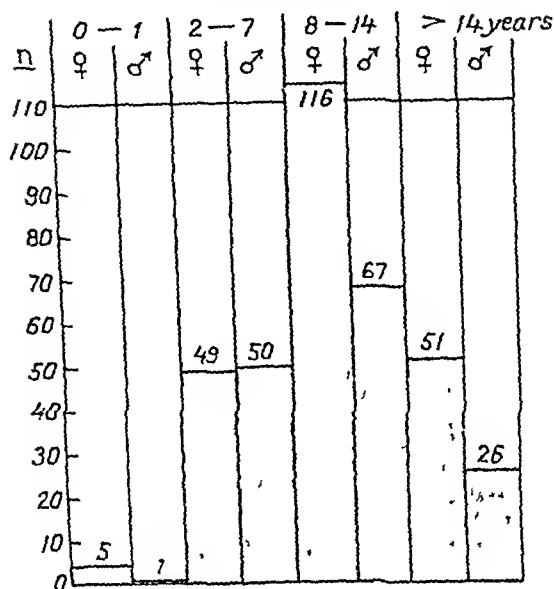


Fig 1—Age and sex distribution

HYPOXIA TOLERANCE TEST

9% O₂ 10'

265 cases

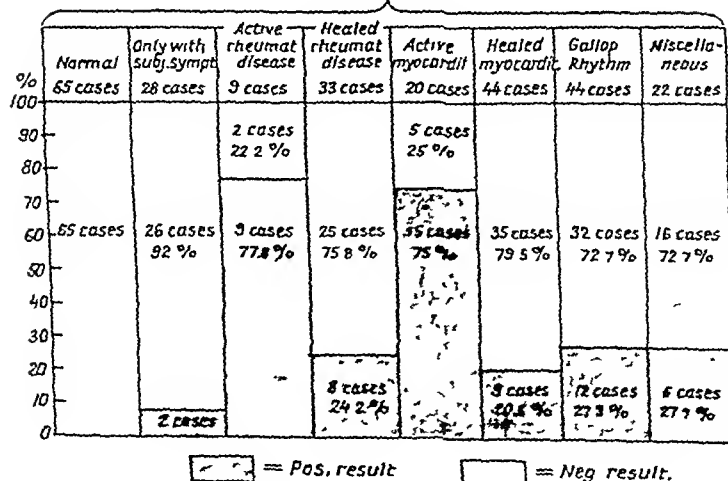


Fig 2—Normal cases and cases of acquired heart disease.

NORMAL CASE 97

Girl, 10 years



Fig. 3.—Normal case, girl, 10 years old.*

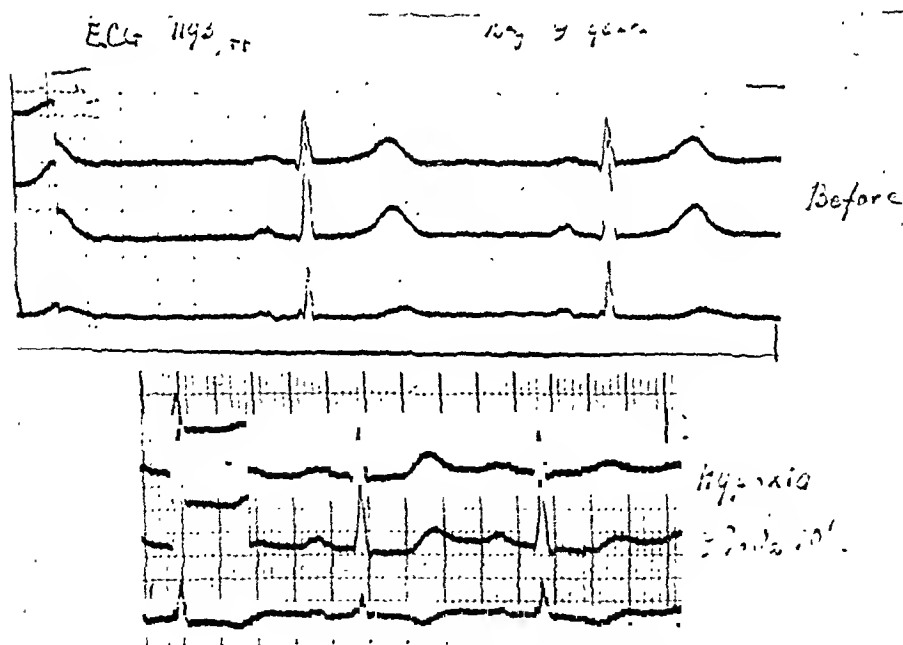


Fig. 4.—Boy 9 years old with acute myocarditis.*

*The time lines on the ECG charts are: thin lines, $\frac{1}{50}$ second, or 0.02; thick lines, $\frac{1}{10}$ second, or 0.1.

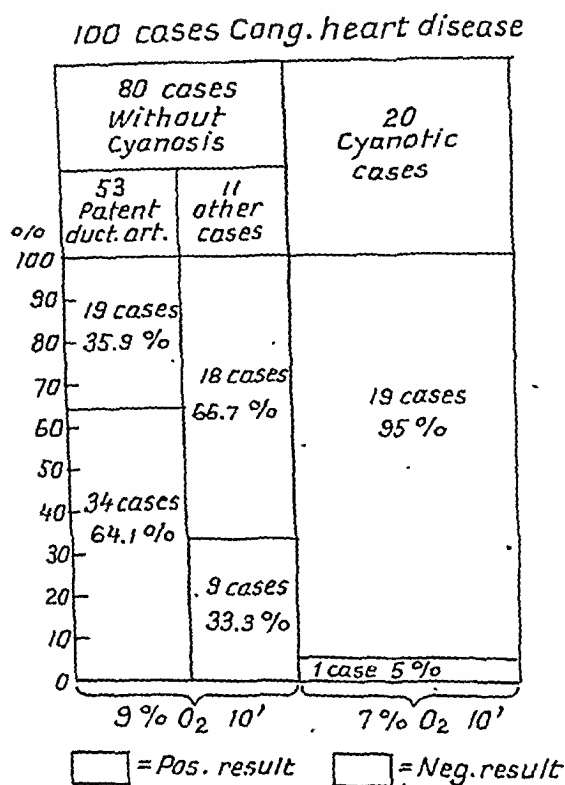


Fig. 5.—Congenital heart defects.

PATENT DUCTUS ARTERIOSUS

Difference before — after op:

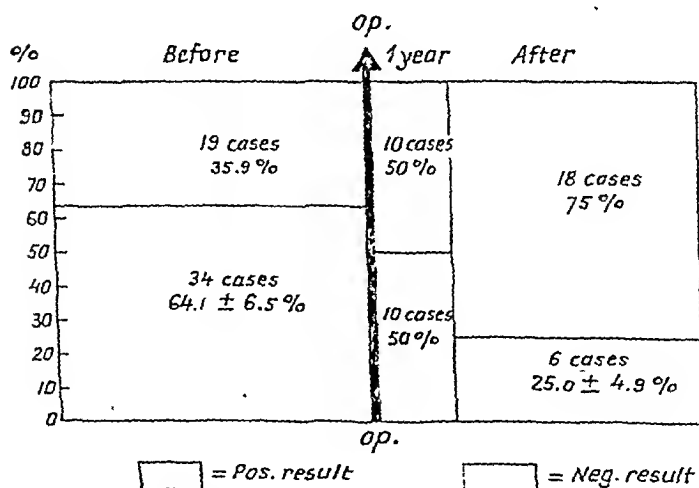
 $D = 39.1 \pm 8.1\%$ (statistically significant)

Fig. 6.—Patent ductus arteriosus. Patients examined before and after operation

sized especially by Carlgren,³ that there is a connection between gallop rhythm and myocardial damage. Finally, there is a group of twenty-two miscellaneous cases, in which 72.7 per cent of the tests were negative.

Fig. 3 presents electrocardiograms in a normal case with negative result of the hypoxia tolerance test. 9 per cent oxygen having been given for a period of ten minutes. Fig. 4 illustrates a case of acute myocarditis with positive hypoxia test. The patient was a 9-year-old boy with fatigue, pallor, enlargement of the left ventricle on x-ray, a slight systolic murmur, and a third sound gallop rhythm, phonocardiographically verified. The electrocardiogram was normal. Two months later the hypoxia test was negative, and the patient no longer showed any cardiac symptoms.

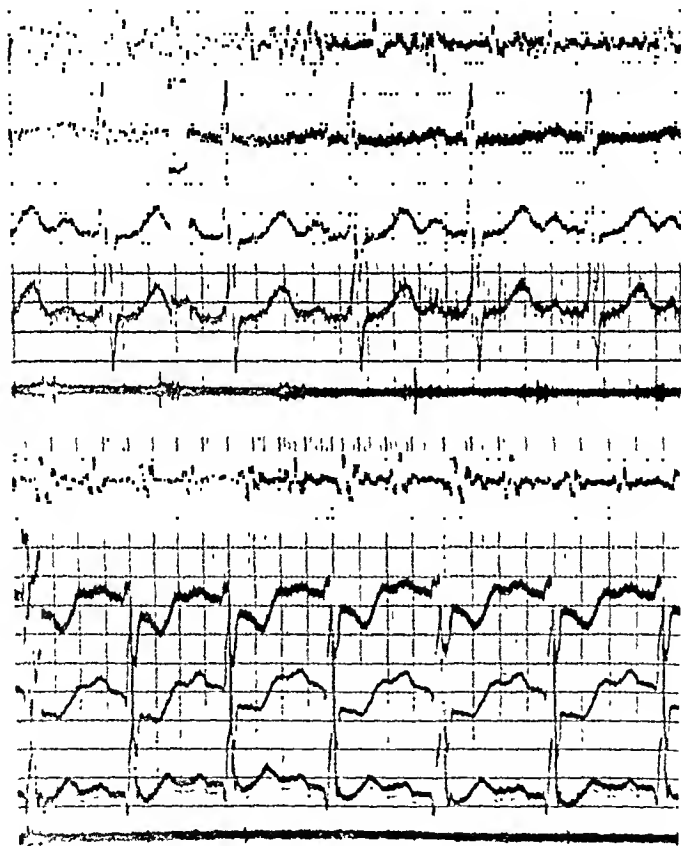


Fig. 7.—Three-year-old girl with patent ductus arteriosus; before operation. Positive result of hypoxia tolerance test.

The studies made in congenital heart disease are brought together in Figs. 5 and 6. Fig. 5 shows eighty cases of heart defects without cyanosis, fifty-three of which are patent ductus arteriosus, and twenty cases of cyanosis. It can be seen that two-thirds of the cases of acyanotic congenital defects which are not

patent ductus, perhaps mostly septal defects, react negatively. However, this group has hitherto not been systematically tested. Therefore it is necessary to wait until more experience is available.

The hypoxia test in "blue babies" has its own history. Most of these patients are small children in a delicate condition. Consequently we began to test them very carefully. At first we gave them 15 per cent oxygen, with no

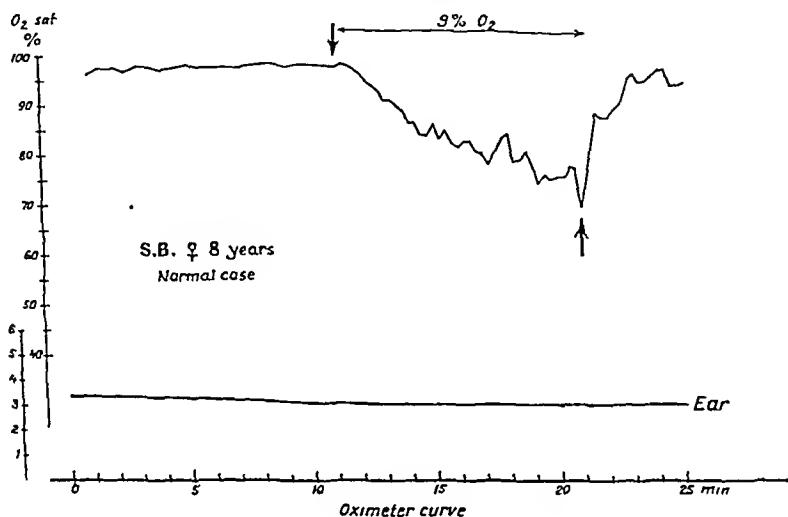


Fig 8—Oximeter curve Arterial oxygen saturation during the hypoxia test in a normal patient

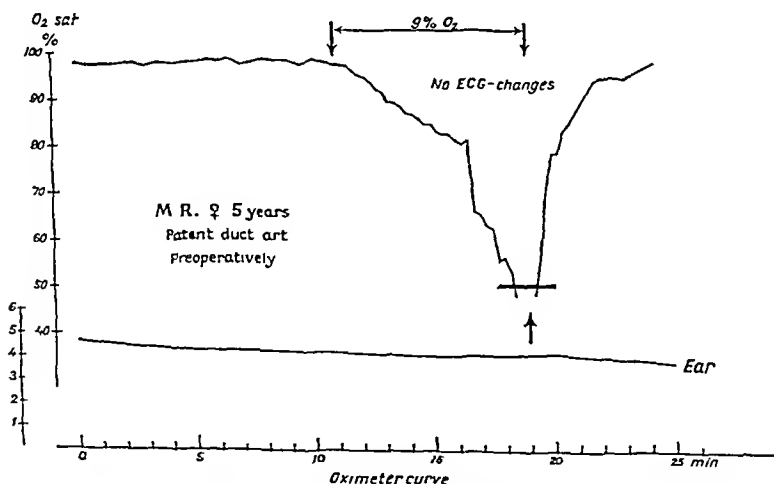


Fig 9—Oximeter curve Arterial oxygen saturation during the hypoxia test in a 5-year-old girl with patent ductus arteriosus

reaction. Some days later we tried 13 per cent, later 11, 10, and finally 9 per cent oxygen. The results were completely negative with no reaction at all. There was no shortness of breath and no marked increase in cyanosis. We then gave 8 and 7 per cent oxygen, a concentration which healthy children have

marked difficulties in tolerating. The same result—no reaction. This fact must signify that the organism in a case of permanent cyanosis is used to the lack of oxygen to such a degree that the normal reflex does not function. It would be of the greatest interest if the "blue babies" reacted positively to the hypoxia test some time after the Blalock-Taussig operation. The time after operation has until now been too short to judge the situation.*

Fig. 6 presents the data on patent ductus arteriosus. Before operation 64.1 per cent gave a positive test. The patients examined more than one year after operation showed quite another result. Only 25 per cent reacted positively. This difference is statistically significant. The twenty patients examined during the first year after the ligation of the ductus take an intermediate position, 50 per cent showing negative and 50 per cent positive reactions. This result illustrates both the improvements made by the operation and the value of the hypoxia tolerance test.

Fig. 7 is recorded from a 3-year-old girl. This was a typical case of patent ductus arteriosus. Before operation she reacted positively to the hypoxia test, as shown by the tracings.

In a few cases we have followed the oxygen saturation during the hypoxia test by means of an oximeter. Figs. 8 and 9 show the tracing obtained in one normal case and in one case of patent ductus arteriosus. The oxygen saturation of the arterial blood falls from 100 to about 70 per cent in a normal child. In the patent ductus patient the oxygen saturation fell much more, in fact so far down that the lowest point could not be determined on the scale. It is of special interest that in this patent ductus case, that of a girl of 5 years, there were no positive signs in the electrocardiogram or the phonocardiogram during the hypoxia test. Further studies in this field will show if this observation is in accordance with a rule or is an exception.

SUMMARY

The hypoxia tolerance test has now been performed in 365 cases with about 600 examinations. In normal cases the reactions are negative with very few exceptions. Active rheumatic carditis and active myocarditis of other etiology give positive results in about three-quarters of the cases. Healed carditis and gallop rhythm give a positive result only in about 25 per cent.

In congenital heart disease, the patent ductus cases as a rule react positively before operation and negatively after the ligation. A few patients were also studied by means of the oximeter during the hypoxia test, making it possible to increase the value of the method. However, more cases must be examined.

Finally, there seems to be no doubt that patients with congenital heart defects and cyanosis do not react at all to the hypoxia tolerance test. This must signify that a child with permanent cyanosis is acclimated to the lack of oxygen and that he is unable to react in a customary way.

*Sixteen patients have, until now, been operated upon in Stockholm (six deaths).

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CONGENITAL TOXOPLASMOSIS

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ALTHOUGH toxoplasmosis has not been frequently reported in human beings, it has recently been brought more to the forefront because of increasing interest in the disease and improved diagnostic methods.

This protozoan parasite was first observed in 1908 by Nicolle and Maneeaux¹ and by Splendore.² It has been characterized^{3, 4} by a world-wide geographical distribution, a pathogenicity for numerous hosts including mammals and birds, and an affinity for many tissues but especially those of the central nervous system. It is crescentic or curved, measures 4 to 7 μ in length and 2 to 3 μ in width, is pointed at one or both ends, and consists of cytoplasm with a rounded chromatin body situated centrally or nearer the blunter extremity. The toxoplasma⁵ is larger and more curved than the encephalitozoon with which it may be confused,⁶ and, unlike the encephalitozoon, is destroyed by freezing, stains deeply with hematoxylin-eosin, has poorly defined individual forms and produces a marked necrotizing reaction, which in the central nervous system is often followed by calcification. In addition, the toxoplasma may at times have to be differentiated⁷ from other protozoan parasites such as the *Leishmania* and that causing avian malaria.

Although the cases reported by Janku⁸ in 1923, Torres⁶ in 1927, and Richter⁹ in 1936 were later classified as probably being of the toxoplasmic group, there was no conclusive report of the parasite's causing disease in human beings until 1939 when Wolf, Cowen, and Paige⁴ proved by transmission of toxoplasmosis to a large number of animals that the parasites found in the granulomatous lesions of a 31-day-old infant who died of widespread encephalomyelitis were of the toxoplasmic group.

Following their report of infantile toxoplasmosis, others discovered it to be the cause of an acute encephalitis in older children³ and of a predominantly pulmonary infection in adults.^{10, 11}

More reports^{7, 12-24} on the infantile type followed, and with further study it was revealed^{14-16, 23} that despite the severity of the disease many patients survived.

By 1946 Pratt-Thomas and Cannon²⁴ had found twenty-one cases of toxoplasmosis proved by autopsy, fifteen of which were in infants, while Callahan, Russell, and Smith⁷ reported on a total of eighteen infantile cases that had had pathologic study; they did not include the case of Pratt-Thomas and Cannon, however. In February, 1947, Miller²³ had found a total of thirty-eight cases and added one of his own to the records.

From the Pediatric Service of the New York Medical College and Flower-Fifth Avenue Hospitals, Dr. Reuel A. Benson, Director.

This case was presented before the Pediatric Section of the New York Academy of Medicine on May 8, 1947.

It is believed^{3, 7, 25} that toxoplasmosis is transmitted to man from a reservoir in lower animals, many of which are domestic. However, in consideration of the positive neutralizing antibodies found in mothers of infants with the disease, it can be assumed that infantile toxoplasmosis can be acquired in utero^{7, 12, 16, 19, 25-27} and that the toxoplasma^{21, 28} probably crosses the placental barrier to infect the fetus. That this is very possible is illustrated by one patient²⁷ with chronic toxoplasmosis in whom each of three pregnancies activated a quiescent chorioretinal lesion, thus bringing up the probability that pregnancy has been an activating factor in some cases of the disease. The final proof of intrauterine transmission would be the finding of toxoplasma in the placenta, but no such verification has been forthcoming up to the present.

However, there is also the possibility that some cases may be acquired post partum since Zuelzer¹⁹ reported one case in which the mother's serum did not reveal any neutralizing antibodies.

The outcome in toxoplasmosis may well depend upon the state of development of the fetus at the time of infection or the number of parasites invading the area, but the clinical course⁷ depends upon the localization of the lesions. Therefore, variants may range from no findings²⁷ to those of the typical case. Some report cases in which no symptoms or signs were ever manifested but in which evidence of the parasite was revealed at necropsy²⁹ or through neutralizing antibody tests.^{16, 21, 23, 27, 30, 31} Others^{25, 27, 32} reveal cases in which only the eyes were involved, and in some cases³ only systemic manifestations were noted. In the cases of human toxoplasmosis reported on to date, there has been noted³ some involvement of the central nervous system with or without lesions in other organs. Furthermore, it is possible that some patients survive infections without important handicaps even if the infection involves the brain and eyes, and there is a probability that a fair number suffer cerebral damage without calcification.

In the typical case, the following criteria^{3, 12, 14, 25} have been listed as necessary for the diagnosis of the infantile type of toxoplasmosis:

1. Infection occurring in utero or shortly after birth with symptoms present at birth or shortly thereafter.
2. Signs of cerebral injury, such as
 - a. Tremors, spastic contractions of extremities, and convulsions;
 - b. Microcephalus or internal hydrocephalus which is clinically evident or demonstrable by pneumoencephalography. The hydrocephalus in 80 per cent of cases is obstructive in type and progressive.
 - c. Mental retardation, which may be present but is not essential, as shown by reports^{16, 21} of some cases in which the intelligence was not affected.
3. Ocular signs such as ocular palsies, microphthalmus, enophthalmos, membranous masses of granulation tissue in the vitreous, and chorioretinitis, especially in the macular region, which consists of slightly depressed or elevated, white or reddish brown, round or oval patches with irregular, spotty black pigmentation. The lesions visible by ophthalmoscopic examination are mainly bilateral and often multiple.

4. Roentgenographic evidence of intracerebral calcification of the irregularly distributed granulomata, which are often bilateral and involve the cerebral cortex and basal ganglia.

5. Xanthochromia, round cell pleocytosis, and high protein content of cerebrospinal fluid, plus the presence of toxoplasma on smear.

6. Recovery of toxoplasma from body fluids, especially from blood or cerebrospinal fluid, by direct smear or by inoculation of mice, rabbits, or both, intracerebrally and intraperitoneally.

7. Demonstration of toxoplasma neutralizing antibodies in the blood of infant or mother as described in the literature.^{27, 30, 31}

Other pertinent findings may be:

1. Neonatal jaundice, which occasionally lasts many weeks and may be due to liver damage¹⁵;

2. Hepatosplenomegaly, which lasts for many months;

3. Interstitial pneumonitis, which has been found in three cases⁷;

4. Occasional anemia and leucopenia with absolute rise in lymphocytes;

5. Variable temperature, which may go from subnormal to elevated.

6. Gastrointestinal symptoms, such as vomiting and diarrhea, which may be initial symptoms of the disease;

7. Myocarditis, which was found at autopsy⁷ in six cases but was not associated with clinical symptoms.

A complement fixation test is being studied but is not yet sufficiently developed to be useful for diagnosis.

The autopsy findings^{3, 4, 12, 13, 24, 25} in typical cases have revealed focal areas of inflammation and necrosis and disseminated miliary granulomas which showed a marked tendency to calcify.

No effective therapy²⁵ has been devised to date. Sulfathiazole and sulapyridine have shown promise in experimental toxoplasmosis but have not been tried in human cases. Penicillin³³ has been found to be ineffective for this type of infection.

Because of the relative rarity of cases of toxoplasmosis and because of the increasing importance of toxoplasma as an etiological factor, it was felt wise to stress the condition by reporting another case.

CASE REPORT

I. L., a 17-month-old Negro female infant was admitted on Dec. 11, 1946, for observation because of loss of weight and mental retardation.

The infant had been full term, and delivery was spontaneous at a local hospital on July 14, 1945, after two hours of labor. The birth weight was 6 pounds and 4 ounces, and on discharge a diagnosis of microcephaly was made.

The family history was essentially negative. All siblings were alive and well. The mother was gravida iii, para iii, and had not had any evidence of illness during her pregnancy.

The baby failed to develop normally both physically and mentally and was referred to the hospital for further study.

On admission, her height was 59 cm. (23¾ inches), her weight 2.7 kg. (6 pounds), and she could neither hold up her head nor sit up. There was generalized spasticity including the neck, back, and all extremities (see Fig. 1). She had a weak cry and appeared

TABLE I. LABORATORY DATA

	DECEMBER		JANUARY		MARCH	APRIL	JUNE
	12	16	15	22	28	11	4
Icteric index		5	4	5	4		5
Van den Bergh		Neg.	Neg.	Neg.	Neg.		Neg.
Cephalin flocculation		Neg.	Neg.	Neg.	Neg.		Neg.
Phosphorus		3.5	3.3	4.5	3.6		4.8
Phosphatase		2.0	4.6	4.0	6.8		10.3
Total cholesterol		346	188	224	248		330
Free cholesterol		108	39	51	67		92
Cholesterol esters		238	149	173	181		238
Total serum protein	6	6.2	7.3	7.6	7.3		8.1
Albumin		4.3	4.7	5.6	4.5		5.4
Globulin		2.9	2.6	2.6	2.8		2.7
A/G ratio		1.5	1.8	1.9	1.6		2.0
RBC (in millions)		7	5.37		4.91		
Hemoglobin		9	9		9.4		
WBC (in thousands)		12	9.25		9.2		9.75
Lymphocytes		82	63		60		61
Polynuclears		12	27		27		39
Mononuclears		4	8		1		
Eosinophiles		2	2		2		
CO ₂ combining power	37				48		
Wassermann (baby)	Neg.						
Wassermann (mother)			Neg.				
Creatinine					1.3		
Urea nitrogen					15		
Rose-Exton test							
Fasting sugar					110		
½ hour after 5 Gm. glucose					130		
1 hour after 10 Gm. glucose					155		
Spinal fluid							
Color		Clear			Clear		
Pressure		170 mm.			Normal		
Cells		0			2		
Sugar		72			55		
Proteins		43			38		
Chlorides		713			704		
X-rays							
Skull		Multiple	Calcified	Areas			
Long bones		Normal					
Chest						Neg.	
Weil-Felix			Neg.				
Widal			Neg.				
Heterophile						1:32	
Urine							
Albumin					+	Neg.	
Sugar					+	Neg.	
Hyaline casts					Occ.	Neg.	
Pitressin test					Neg.	Neg.	

TABLE II. HEIGHT AND WEIGHT PROGRESS

	DEC. 11	JAN. 5	MARCH 25	APRIL 21	JUNE 4
Length (cm.)		59	59.4	60.6	62.5
Head to pubis		34	35	35.6	37.5
Pubis to heel		25	24.4	25	25
Chest (cm.)		40	43.8	43.8	45.0
Abdomen (cm.)		37	41.3	41.3	41.3
Occipitofrontal circumference		34	36.3	36.3	36.3
Weight (kg.)	2.7		5.6	5.7	6.5

marasmic. The mucous membranes were dry as was the skin, which was also sealy and hung in loose folds. The hands and feet were swollen and bright pink in color.

The head was microcephalic with the occipitofrontal circumference measuring 34 cm. ($13\frac{1}{4}$ inches), and all the fontanels were closed. There was a rotary nystagmoid movement of the eyes, a high arched palate, and only one upper and two lower central incisors had erupted.

The heart, lungs, and abdomen did not reveal any abnormalities.

Blood Wassermann tests done on the baby and her mother were negative, and both of them were Rh positive, Type O.



Fig. 1.—Sitting position, revealing marked spasticity and microcephaly.

Weil-Felix, Widal, and brucellosis tests were negative, while the heterophile antibody reaction was positive only in 1:32 dilution.

A blood count on December 18 revealed an anemia, polycythemia and lymphocytic leucocytosis, but by January 8, the blood count was markedly improved and continued so. Total serum proteins at first were low and the total cholesterol high, but when repeated on January 15 and 22 they had become normal.

A spinal tap done on Dec. 16, 1946, revealed clear fluid, no increase of pressure, no cells, protein 43 mg., sugar 72 mg., and chlorides 713 mg.

On Dec. 17, 1946, an x-ray of the skull revealed diffuse areas of calcification (Fig. 2), at which time a tentative diagnosis of toxoplasmosis was made. X-rays for bone age and pathologic conditions of the chest did not reveal any abnormalities. On December 18, the ophthalmologist reported diffuse bilateral chorioretinitis on fundus examination.

In view of these findings, blood was obtained for inoculation into mice and rabbits, but no toxoplasma was found. Spinal fluid was also injected into these animals, but again no evidence of the parasite was detected. Neutralizing antibody tests* done on the infant's blood were negative.

*The neutralizing antibody tests were done through the courtesy of Dr. D. Cowen of the Medical Center, New York City.

During her stay in the hospital, the baby improved, her weight increasing from 2.7 kg. (6 pounds) to 6.5 kg. (14 pounds) and her height from 59 cm. (23¼ inches) to 62.5 cm. (25 inches). (See Tables I and II.)



Fig. 2.—X-ray of skull. Note multiple intracerebral calcifications.

DISCUSSION

Although most of the cases reported have occurred in the white race, this is the third case found in the Negro race, two others^{12, 19} having been reported previously.

Up to the present time, more females have been affected than males. However, as pointed out by another writer,⁷ the cases are too few as yet to consider that sex plays any part in the picture.

In the case presented here the essential clinical features listed as necessary for the diagnosis of infantile toxoplasmosis were present, namely:

1. Microcephalus,
2. Chorioretinitis.
3. Diffuse cerebral calcification,
4. Mental deficiency.

Of the cases previously reported, only two¹² were recorded as microcephalic, and in two others^{15, 21} the heads were slightly smaller than normal. The present case was definitely of the microcephalic type, and even at present the occipitofrontal circumference is only about two-thirds of normal size.

An unusual feature noted in this case was the marked longitudinal shortening, with the height on admission being the equivalent of that of a 3-month-old infant. Even now it is only about two-thirds normal. Since the dwarfism is of the uniform type, it can be surmised that the pituitary may have been involved in the process with the generalized shortening as a result. In substantiation of this is the fact that moderate atrophy of the sella turcica¹³ has been noted in one previous case.

Regarding the inability to isolate the parasite from the blood or spinal fluid, it must be remembered²⁵ that in some older infants and children the toxoplasma may still be present and active, but in many cases the lesions may represent only the residual of a previous infection which has subsided. As a matter of fact, Sabin³ reported negative results when he inoculated mice with spinal fluid and blood obtained on the tenth day of the disease, and in Miller's²³ case also no parasite was found in the spinal fluid.

Concerning the neutralizing antibodies, writers^{3, 14, 32} have found that these antibodies disappear as early as the sixth week after the infection, and therefore the optimum time for taking the test would be in the first three to four weeks after the onset of the disease. Moreover, while a positive neutralizing antibody test is strong evidence in favor of toxoplasmic infection past or present, a negative result³⁴ does not eliminate the possibility of its having been present and subsided.

However, since our patient manifested all the clinical criteria necessary, it can be assumed that this was a typical case of toxoplasmosis.

SUMMARY AND CONCLUSION

1. A case of congenital toxoplasmosis in a 17-month-old Negro female infant is reported.

2. Microcephalus, chorioretinitis, diffuse cerebral calcification, and mental deficiency were all present.

3. Dwarfism was noted for the first time in this condition.

4. In late cases toxoplasma may not be isolated.

5. A negative neutralizing antibody test after the fourth week of illness does not nullify the diagnosis.

6. The discovery of toxoplasma as a cause of mental deficiency and encephalomyelitis adds another causative agent to be considered in these conditions. Furthermore, since cases of toxoplasmosis arise as a result of placental transmission, prophylaxis would depend upon the early diagnosis of the condition in the pregnant mother. Following its diagnosis, an effective method of destroying the parasite must be found. Since the number of reports of the infection are increasing as it is better understood and being watched for, it is of the utmost importance to endeavor to prevent its occurrence in infants through early detection in the mother.

Therefore the problem presenting itself is that of devising a simple diagnostic test and also of securing an effective therapy to eliminate the infection before it has produced permanent changes.

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THE TREATMENT OF TUBERCULOUS MENINGITIS

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IN 1945, Feldman and Hinshaw¹ showed that streptomycin suppressed tuberculosis in guinea pigs, and experiments on human beings seemed to show similar effects.² Since that time, streptomycin has been used for all types of tuberculosis and found to be of definite value as an adjuvant treatment for acute miliary tuberculosis, tuberculous meningitis, and prior to operations on tuberculous chests.

Its use in miliary tuberculosis is hopeful.³ Early, fine tuberculous lesions respond much more favorably than do older fibrocaseous lesions.⁴ Hinshaw and his associates⁵ treated twelve patients with miliary tuberculosis and tuberculous meningitis. Six patients expired; five patients survived from two to ten months. Symptomatic response was observed after one to two weeks of therapy, and in certain cases there was clinical, roentgenographic, and histopathologic evidence of healing, but there were no actual cures. All patients treated continued to show slight abnormalities in the spinal fluid, such as an elevation of protein and cells at the time of discontinuance of the drug. It has been further shown⁶ that streptomycin has only a suppressive, inhibitory action on tuberculosis with a tendency to recurrence of symptoms following termination of treatment.

Our paper includes the reports of nine patients ill with tuberculous meningitis, who were treated with streptomycin. Marked improvement was obtained in two individuals, but the eventual outcome is not known. The protocols of these nine cases are as follows:

CASE REPORTS

CASE 1.—C. P., a 4-year-old white girl, was admitted to the Department of Contagious Diseases of City Hospital on Dec. 19, 1946, acutely and seriously ill. The illness dated back to September, 1946, when the child became anorexic, slept poorly at night, was restless, and failed to gain weight. This continued until December, 1946, when the malaise became prominent, she did not play normally, and the anorexia became pronounced. On December 8, a cough and a slight fever occurred. By December 11, the cough was worse and a temperature of 38° to 39° C. was noted. These symptoms remained unchanged until December 16, when the respirations became rapid. On December 19, meningitis was recognized, and she was admitted to the hospital.

The child had always been well except for measles at 3 months of age and pertussis at 2 years of age. During the previous year, she had occasionally stayed with an aunt who had a chronic cough supposedly due to carcinoma of the lung and who died shortly before the patient became ill.

Physical examination revealed a well-developed but poorly nourished white girl. She was lethargic, had cyanosis of the lips and finger tips, and her face had a dusky, pale appearance. She was acutely ill. The temperature was 38.9° C.; pulse 110; respirations rapid and shallow, 60 per minute, with

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occasional grunting and a hacking cough. Fine moist râles were heard throughout the right chest with no discernible dullness; the left chest was clear to percussion and auscultation. The abdomen was tender throughout, and the spleen was palpated two fingerbreadths below the left costal margin. The neck was rigid to anterior flexion, and the Kernig sign was positive. Examination of the blood disclosed 15.0 Gm. of hemoglobin, a red blood cell count of 4.30 million, and a white blood cell count of 10,600 with 83 per cent polymorphonuclears and 17 per cent lymphocytes. The urine was normal. A lumbar puncture revealed clear cerebrospinal fluid containing 36 cells, 96 per cent lymphocytes and 4 per cent polymorphonuclears, and a four plus reaction to the Pandy test. The protein was 80 mg. per 100 c.c.; sugar 30 mg. per 100 c.c.; chloride 423 mg. and sodium chloride 699 mg. per 100 c.c. The qualitative five-tube sugar test showed no reduction in any of the five tubes.

X-ray examination of the chest revealed numerous minute, soft, discrete nodulations throughout both lung fields consistent with a diagnosis of diffuse, hematogenous, pulmonary tuberculosis.

A diagnosis of acute, diffuse, hematogenous tuberculosis with tuberculous meningitis was made, and the patient was given daily 1.2 Gm. of streptomycin intramuscularly in divided doses along with 5.0 Gm. of Promin intramuscularly.

During the first week, the patient was in a precarious condition. The temperature fluctuated between 38.5° and 40.0° C.; the pulse and respirations were elevated. She remained cyanotic, ate poorly, and continued to lose weight. On the fourteenth hospital day, slight distention of the abdomen was found. The abdomen was doughy, and no fluid wave was demonstrable. The examiners thought that she now showed clinical evidence of tuberculous peritonitis.

A repeat x-ray examination of the chest about this time showed no significant change in the pulmonary disease since the initial examination. Throughout the early weeks, the patient continued to have cyanosis and was very inactive, refusing to sit up or play with her toys. Food and fluids were taken poorly, necessitating parenteral fluids to meet the daily requirements. The temperature began to fall slightly, after three weeks, to 38° C., but the pulse remained rapid, 110 per minute, and the respirations remained at from 50 to 60 per minute. There was no significant change in the cerebrospinal fluid.

During the subsequent four weeks, progressive improvement was noted. The temperature, pulse, and respirations returned to normal and remained so. Radiographs of the chest showed progressive diminution in the density of the pulmonary lesions. The cerebrospinal fluid sugar and chlorides began to rise to the normal range, but there was still an increase in the amount of protein and cells. Cyanosis was less marked, and the child became more active, showing much more interest in her surroundings. Her appetite increased, although her weight remained stabilized.

About the seventh week, the patient was markedly improved clinically. The abdominal distention had receded; the cyanosis had completely disappeared; the neck was no longer stiff; and the chest was clear to physical examination. Food and fluids were taken well. The weight which had decreased about four pounds during her illness began to return slowly. Promin was discontinued on the sixtieth hospital day and streptomycin was continued.

For the remaining twelve weeks, there was an uneventful course. Films of the chest continued to show clearing of the nodular shadows. There were no signs of mental retardation. The temperature, the pulse, and the respirations remained normal, and on the one hundred thirty-fourth hospital day, streptomycin, a total of 159.2 Gm. of which had been administered, was discontinued. For three weeks following, the patient was closely observed for changes in her condition, and since none was noted and the chest film showed complete clearing

of the miliary shadows (although the cerebrospinal fluid still contained 28 cells, all of which were lymphocytes, and 55 mg. of protein), she was discharged on the one hundred fifty-third hospital day.

Spinal fluid and gastric washings obtained on admission were inoculated into guinea pigs. The animal inoculated with the gastric washings died several days later and no conclusion was obtained, but the one inoculated with the spinal fluid was sacrificed after six weeks and found to have diffuse tuberculous lesions from which the tubercle bacillus was recovered.

The patient was followed at weekly intervals subsequently, and she continued to show improvement in weight, appearance, and activity for three weeks. During the fourth week, however, fever and anorexia were noted, and the patient was readmitted to the hospital on June 25, 1947.

This time the spinal fluid contained 330 cells, 100 per cent of which were lymphocytes; the protein was 180 mg. per 100 c.c.; the chlorides and the sugar content were within normal limits. The temperature was 39° C., and the patient appeared lethargic and chronically ill.

X-ray examination showed complete resolution of the previous pulmonary infiltration.

Streptomycin was again administered, and the dose was raised to 3 Gm. per day in divided doses. Her general condition has remained poor, and at the present writing, the sixty-second hospital day of the patient's second admission, the temperature still fluctuates between 37° and 38° C. The present cerebrospinal fluid shows an increase in cells (850 lymphocytes) and protein (280 mg.) despite continued therapy. (She died on Dec. 18, 1947.)

CASE 2.—J. N., an 18-month-old white, male infant, was well until the latter part of October, 1946, when he had a fever and cough which were treated as acute bronchitis. He recovered promptly and remained well until Feb. 13, 1947, when he had a second attack of fever with a cough. Restlessness and irritability were noted, the child cried continuously, and he slept poorly at night. He was treated with sulfadiazine without result. On February 15, he became listless and lethargic, refused feedings, and developed a stiff neck. On the following day symptoms continued unabated, and he was admitted to the hospital.

Physical examination revealed an acutely ill, lethargic, and dehydrated infant lying in an opisthotonic position. The temperature was 38.5° C., the pulse 120, and the respirations 88. There was marked nuchal rigidity. Respirations were rapid and shallow and out of proportion to the fever, but there was no cyanosis or dullness to percussion. Occasional râles were heard at the right base, posteriorly. The Kernig and Brudzinski signs were positive.

Lumbar puncture was performed, yielding slightly cloudy spinal fluid containing 520 cells with 95 per cent lymphocytes and 4 per cent polymorphonuclears. The Pandy test was four plus. The protein content was 300 mg. per 100 c.c., sugar 25 mg. per cent, and sodium chloride 673 mg. per cent. Direct smear of the fluid showed acid-fast organisms identified morphologically as *Mycobacterium tuberculosis*.

X-ray examination of the chest showed dense, mottled infiltrations extending from the hilus to the bases bilaterally with tiny nodular shadows scattered throughout the lung fields, consistent with the diagnosis of miliary tuberculosis.

A diagnosis of miliary tuberculosis with tuberculous meningitis was made, and daily streptomycin therapy was instituted. One gram of streptomycin intramuscularly and one gram of promin intravenously were given.

A tuberculin test made on admission with old tuberculin, 1:1,000 dilution, was negative. When repeated four days later with 1:100 dilution, the reaction was faintly positive.

During the first two weeks of treatment, the patient did poorly. The fever fluctuated to 39° C. daily, the pulse rate ranged from 100 to 130 per minute, and respirations remained about 30 to 40 per minute. He remained in an opisthotonic position continually, had a high shrieking cry, and developed a divergent strabismus of the right eye. The eye grounds were normal, but the child complained that the "lights were out." He fumbled for his toys and bottle, as if blind, and beginning hydrocephalus was suspected. Pneumoencephalograms were performed which showed air in the basal cisterns, but no air was visualized in the ventricles, possibly due to blockage in the region of the fourth ventricle. By the fifth hospital week, the temperature began to stabilize, rising only to 37.8° C. daily; the respirations became normal but the pulse rate remained rapid, ranging from about 110 to 120 per minute. Cerebrospinal fluid findings showed definite improvement with a decrease in number of cells (50) and a rise in sugar (52. mg.) and chlorides (426 mg. of chloride and 704 mg. of sodium chloride).

The patient continued to improve as evidenced both clinically and roentgenologically. Follow-up films of the chest showed gradual progressive resolution of the mottled infiltrations in the lungs. Promin was discontinued on the sixty-ninth hospital day, but streptomycin was not discontinued until the eighty-seventh hospital day. At that time, the spinal fluid still contained 43 lymphocytes. The proteins were 120 mg. per 100 c.c., sugar 67 mg. per 100 c.c., chlorides 439 mg., and sodium chloride 724 mg. The temperature, the pulse, and the respirations remained normal, and the baby seemed to be markedly improved. He ate well and gained about four pounds. The eye grounds failed to show tubercles, optic atrophy, or papilledema, but vision was still diminished. The patient was more active and played with his toys, and his appetite was good. No obvious mental deterioration was noted, and the child's vocabulary increased steadily in keeping with his age.

The patient remained in the hospital for fifty days after the discontinuance of streptomycin and continued to show a good clinical response. He seemed to be alert mentally and appeared healthy and happy. He had gained the weight he lost in the early period of his illness and weighed 30 pounds at the time of discharge. Vision did not return, and light perception was all that remained. The spinal fluid continued to show a slight increase in proteins and cells. His hearing was good, and there was no evidence of vestibular damage. The patient was discharged markedly improved on the one hundred thirty-first hospital day, having received a total of 86 Gm. of streptomycin, but the prognosis is still guarded.

CASE 3.—C. W., a 9-year-old white boy, was apparently well until April 26, 1947, when he began to complain of intermittent headaches and anorexia. On May 1, he had malaise, became nauseated and vomited, and had a temperature of 39° C. On May 3, his temperature varied from 39° to 39.5° C., and he received penicillin. For the next several days, he became increasingly lethargic and his headache more severe. On May 8, he attended school but was sent home because of drowsiness. Three days later, he became delirious, sweated profusely, was very lethargic, and was admitted to the Department of Contagious Diseases. There was no known exposure to tuberculosis.

On physical examination, the temperature was 38.5 C., pulse 150 per minute, and respirations 35 per minute. The patient was a well-developed, well-nourished boy, who was semicomatose but responded to noxious stimuli. The neck was stiff and resisted anterior flexions, positive Kernig and Brudzinski signs were present, and the chest was clear to percussion and auscultation. The remainder of the physical examination was negative.

The cerebrospinal fluid had normal dynamics. It contained 342 cells, 50 per cent of which were lymphocytes and 50 per cent polymorphonuclears; the reaction to the Pandy test was four plus; proteins were 360 mg. per 100 c.e., sugar 46 mg., chlorides 371 mg., and sodium chloride 612 mg.

X-ray examination of the chest showed no evidence of pulmonary infiltration. The patient was given one gram of streptomycin intramuscularly daily in divided doses.

A tuberculin test with old tuberculin (1:1,000 dilution) was very strongly positive.

The patient remained in critical condition throughout his hospital stay. The coma deepened and he showed increasing, generalized muscular spasticity. His arms remained stiff at his sides and resisted bending; the hands remained clenched and flexed sharply at the wrists. The legs also showed an increase of muscle tone, and the feet were held in forcible plantar flexion. Reflexes were all normal.

Streptomycin was continued for six weeks without clinical improvement. Repeat films of the chest showed prominent hilar markings which were thought to represent a tuberculous process, but no pulmonary infiltration was present.

Cerebrospinal fluid continued to show an elevation in cells (264, with 85 per cent lymphocytes and 15 per cent polymorphonuclears). Spinal fluid proteins had risen to 1,440 mg. per 100 c.e., and chlorides remained low (405 mg. as chloride and 668 mg. of sodium chloride).

Although streptomycin was continued, the child's condition gradually became worse. The temperature remained about 40° C., and the patient finally expired on the fifty-first hospital day.

Guinea pigs inoculated with spinal fluid were sacrificed, and *Myc. tuberculosis* was identified in the lymph glands.

Autopsy revealed multiple tuberculous foci throughout the meninges and brain.

CASE 4.—On May 7, 1947, B. W., a 3-year-old Negro boy, had fever and was restless and irritable. He continued to have a daily rise in temperature, particularly in the evening. By May 21, he began to cough, and his attending physician made a cutaneous tuberculin test, which was negative. On May 24, the child vomited, and the mother noticed that the left eyelid drooped. Vomiting, fever, and irritability continued, and on May 28 he was admitted to the hospital.

Physical examination revealed the temperature to be 37.6° C., the pulse 52, and the respirations 36 per minute. The patient appeared acutely ill and very irritable, and he assumed an opisthotonic position. There was ptosis of the left eyelid with bilateral edema of both lids, slight divergent strabismus of the left eye, and a serous discharge from the nose with a postnasal discharge. The neck was slightly resistant to anterior flexion; the abdomen was moderately distended, and the liver was palpated 2 cm. below the costal margin.

Lumbar puncture revealed clear fluid containing 13 cells, 80 per cent of which were lymphocytes. The reaction to the Pandy test was four plus. The protein level was 36 mg. per 100 c.e., the sugar 15 mg. per 100 c.e., and the chlorides 410 mg. per 100 c.e.

An x-ray examination of the chest showed numerous irregularly shaped areas of increased density throughout both lung fields, consistent with a diagnosis of diffuse, hematogenous tuberculosis.

A diagnosis of miliary tuberculosis with tuberculous meningitis was made, and streptomycin therapy was initiated. He received one gram of streptomycin intramuscularly daily.

The patient remained irritable, restless, and anorexic for several weeks, and the temperature had a spiking course, rising to 39.5° C. every afternoon. A repeat examination of the spinal fluid one week after streptomycin therapy was initiated showed no change in the findings except a rise in the sugar content to normal.

The guinea pig inoculation was positive.

By the third hospital week, the patient's condition was improved. The restlessness and the irritability diminished. The ptosis of the left eyelid disappeared and the strabismus diminished. The patient regained his appetite, but his weight remained unchanged.

By the seventh week of treatment, chest films began to show significant clearing of the military lesions in the lungs. Repeat examination of the cerebrospinal fluid showed 68 cells; protein was 130 mg., and chlorides were 445 mg. as chloride and 734 mg. as sodium chloride per 100 c.c.

At the present time, the temperature is still elevated to 38° C. and the blood sedimentation rate is 27 mm. in one hour. Although improvement has been shown clinically and roentgenologically with the use of streptomycin, the period of observation has been too short to draw any conclusions.

CASE 5.—J. C., a 19-year-old Negro boy, first became ill on April 2, 1947, when he began to have frontal headaches, a cough productive of small amounts of green sputum, and a slight fever. This lasted about one week.

In May, there was a recurrence of these symptoms of about the same duration, and on July 7, 1947, there was another episode of frontal headache, weakness, and fever plus constipation. The patient remained in bed nineteen days and finally returned to work. He had lost about 30 pounds of weight since April. In August, frontal headaches recurred and were located directly over both eyes. These were constant and were not relieved by aspirin. They continued unabated, becoming more intense, and on August 16, the temperature was 39° C. and he vomited. The vomiting and the headache continued, and two days later pain in the back of the neck was noted. This became more severe, and he was admitted to the medical department of City Hospital on Aug. 19, 1947.

Physical examination revealed a well-developed and poorly nourished Negro male, who appeared to be moderately ill and showed signs of recent weight loss. The temperature was 39.6° C., pulse 80, respirations 18, blood pressure 122/74. With the exception of a stiff neck, fever, and irritability, no abnormalities were found.

The lumbar puncture revealed clear fluid under normal pressure containing 217 cells, 80 per cent of which were lymphocytes and 20 per cent polymorphonuclears. The reaction to the Pandy test was one plus; protein was 65 mg. per 100 c.c., sugar 31 mg. per 100 c.c., chloride 470 mg., and sodium chloride 775 mg.

X-ray examination showed slight nodular infiltration in both apices and subapical regions, suggestive of bilateral minimal pulmonary tuberculosis.

The tuberculin test was positive in first-strength P.P.D. The diagnosis was pulmonary tuberculosis with tuberculous meningitis, and the patient was transferred to the Department of Contagious Diseases for streptomycin therapy. A dosage of 2 Gm. per day intramuscularly was started.

For the first week, the patient had an irregular temperature ranging from 38° to 41° C., which gradually changed to a daily spiking fever. The patient remained lucid and well oriented, but the headaches remained severe enough so to require Demerol to control the pain. By the second week, the temperature had stabilized at 38.5° C. where it has remained to date. On three consecutive occasions, 100,000 units (0.1 Gm.) of streptomycin were given intra-

theally and were well tolerated by the patient. This has had little effect on the cerebrospinal fluid as it continued to show an increase in cells and protein above the normal limits.

At the present time (Jan. 27, 1948), the patient seems to be doing well clinically. His headaches have subsided, his neck is no longer stiff, irritability has decreased, appetite has increased, and his mental status is good.

CASE 6.—H. P., a 35-year-old Negro man, had tuberculosis and silicosis for three years and was in a sanatorium from January, 1946, until April, 1947, when he left without permission. X-ray examination at that time showed fine, diffuse nodulations throughout both lung fields. He also developed renal tuberculosis and tuberculous epididymitis. The diagnosis was chronic miliary tuberculosis with renal tuberculosis and tuberculous epididymitis.

Following his voluntary release, he remained at home and seemed to do well until approximately two weeks before admission when he began to have headaches with chills and fever. One week before admission, he vomited and noticed a stiff neck. Although he remained lucid, he gradually became lethargic. On the day prior to admission he became confused, argumentative, and incoherent, and lethargy was pronounced. This continued unabated, and he was admitted May 17, 1947, to the Department of Contagious Diseases with tuberculous meningitis.

Physical examination revealed a fairly well-developed and poorly nourished male, who was very confused and disoriented. The temperature was 38° C., the pulse 80, and the respirations 22. The chest revealed dullness in the left axillary space; the breath sounds were vesicular throughout, but fine râles were heard throughout both lung fields. No areas of consolidation or cavitation could be determined. The neck was rigid to anterior flexion, Kernig and Brudzinski signs were positive, and no pathologic reflexes were obtained.

The urine was cloudy and contained three plus albumin, 5 to 6 white blood cells per high power field, and was loaded with granular casts. No red blood cells were present.

The cerebrospinal fluid was clear and contained 147 cells, 50 per cent of which were lymphocytes and 50 per cent polymorphonuclears; the Pandy test was four plus, Ross-Jones four plus, protein 90 mg., sugar 50 mg. per 100 c.e., 405 mg. of chloride, and sodium chloride 668 mg. No bacteria were seen.

X-ray examination of the chest showed multiple tiny nodular shadows throughout both lung fields, consistent with miliary pulmonary tuberculosis.

The patient was placed on daily doses of 2 Gm. of streptomycin intramuscularly. There was no noticeable improvement in his condition and, despite therapy, he remained in a critical condition with a fever ranging between 38° and 39° C. The mental confusion and the disorientation remained unchanged. Kernig and Brudzinski signs were consistently present, and after one month, the cerebrospinal fluid continued to show an abnormal increase in cells (240 cells, 100 per cent lymphocytes) and a protein content of 180 mg. per 100 c.e.

A total dose of 150 Gm. of streptomycin was administered, but at no time during the hospital course was improvement noted. On the seventy-ninth hospital day, the fever rose to 41° C. and the patient expired.

CASE 7.—G. B., an 18-year-old Negro boy, was admitted to the Department of Contagious Diseases on Nov. 6, 1946, having been transferred from another hospital with a diagnosis of tuberculous meningitis.

Three months prior to admission, the patient had become short of breath and had lost considerable weight. One month prior to admission, he had developed a cold with a cough which lasted for one week. Following this, he noticed pain in the left chest which increased on inspiration and seemed to "cut

off his breath." Twelve days before admission, he complained of frontal headache, fever, and vomiting and was taken to another hospital. While in the hospital, the patient's symptoms became progressively worse, and he finally became semicomatose and delirious. His eyes became crossed, the vomiting continued, and stiffness of the neck occurred. A lumbar puncture was performed, and he was transferred to the Contagious Department.

Physical examination revealed a poorly nourished Negro male, who was semicomatose, with a temperature of 39.5° C., a pulse rate of 160 per minute, and respirations of 32 per minute. The blood pressure was 150 systolic and 100 diastolic. The neck was rigid to anterior flexion. There was dullness at the right base posteriorly with decreased fremitus. There were positive Kernig and Brudzinski signs.

X-ray examination of the chest showed a dense homogeneous shadow at the right base extending upward along the right lateral chest wall consistent with pleural effusion. No pulmonary infiltration was present.

Lumbar puncture revealed slightly opalescent fluid under normal pressure, containing 78 cells (85 per cent lymphocytes and 15 per cent polymorphonuclears). The Pandy test was four plus. By direct smear, several organisms were seen and identified morphologically as *Myco. tuberculosis*. The cerebrospinal fluid protein was 180 mg., sugar 33 mg., chlorides 400 mg., and sodium chloride 668 mg.

Guinea pig injection was positive for tubercle bacillus.

The diagnosis was tuberculous pleurisy with effusion and tuberculous meningitis.

Four grams of streptomycin administered intramuscularly and 0.1 Gm. of streptomycin intrathecally were given daily, together with 5 Gm. of promin every four hours.

On the second hospital day, a thoracentesis of the right side was performed, and 50 c.c. of straw-colored fluid were obtained, free of bacteria and tubercle bacilli.

During the first three days of therapy, the temperature fell toward normal and the patient became more lucid. This was for a short period, however, for he gradually lapsed into coma by the eighth hospital day and expired on the twelfth hospital day, having received a total of 36.5 Gm. of streptomycin intramuscularly and 1.1 Gm. intrathecally. The total dose of promin was 200 Gm.

CASE 8.—P. F., an 8-year-old white girl, was admitted to City Hospital on May 26, 1947, with a diagnosis of tuberculous meningitis.

The patient had been well until April 15 when she returned from school with a severe headache located behind both eyes. She also vomited. The vomiting and headache continued for several days, and she was admitted to another hospital, where x-rays and lumbar puncture were performed. A presumptive diagnosis of tuberculous meningitis was made and streptomycin initiated for five days. The exact dose was not obtainable. She seemed to respond well to treatment and was discharged six days later. While at home, she became progressively worse, having periods of mental confusion and vomiting, and on the evening of May 21, she began to have convulsions with rapid shaking movements of the arms and legs. This attack lasted several minutes and during the next few days was repeated many times. The patient finally lapsed into coma and was admitted to City Hospital.

Physical examination revealed a temperature of 38° C., pulse 120 per minute, respirations 22 per minute. The patient was an emaciated, weak, lethargic girl, who when aroused complained bitterly of generalized pains. Her neck was rigid, and Kernig and Brudzinski signs were positive. The remainder of the examination was negative.

Lumbar puncture revealed slightly cloudy spinal fluid containing 1,530 cells, 28 per cent of which were lymphocytes and 72 per cent polymorphonuclear cells. Protein was 178 mg. per 100 c.c.; sugar was 25 mg. per 100 c.c. *Mycob. tuberculosis* was identified by direct smear from a pellicle by acid-fast stain.

X-ray examination of the chest revealed the presence of small, calcific, oval shadows in the periphery of both lung fields, which appeared to be healed tuberculous foci bilaterally.

The patient was immediately started on one gram of streptomycin intramuscularly in daily divided doses. The temperature remained elevated to 38.5° C., and the pulse rate ranged between 110 and 120 per minute throughout her hospital stay. She did not respond to therapy, the coma gradually deepened, and the respirations finally ceased. Despite stimulants and artificial respiration, the patient expired on the tenth hospital day. She had received 9.5 Gm. of streptomycin on this admission.

The findings at autopsy verified the diagnosis of tuberculous meningitis.

CASE 9.—J. B., a 13-year-old Negro boy, was admitted to the Department of Contagious Diseases on Aug. 29, 1947.

Three weeks prior to admission to the hospital, he began to complain of headaches and had malaise and fever. He became lethargic and remained at home. He did not play as usual. The headache was continuous, bilateral, and associated with neck pain. There was an afternoon rise in temperature each day. About two weeks prior to admission, he began to sleep all day. He had anorexia, and he became delirious on the day of admission. He was restless, dyspneic, and acutely ill with signs of meningeal irritation and some ptosis of the left eyelid.

Streptomycin therapy was started on September 4. He was given 2 million units of streptomycin intramuscularly, 1.5 Gm. of sulfadiazine, 5 c.c. of promin intravenously, and approximately 300,000 units of penicillin daily. He developed a right sixth nerve palsy on September 18. The patient's temperature the last forty hours mounted to 43° C. He expired on Sept. 21, 1947.

The urine was clear at all times. The lumbar puncture showed 237 cells and a Pandy test of four plus on August 29; on September 21, there were 230 cells and the Pandy test was four plus; on September 11, there were 130 cells and the Pandy test was four plus; on September 15, there were 464 cells (all mononuclears) and the Pandy test was four plus. The spinal fluid sugar went as low as 17 mg. per cent. Concentration tests for organisms in the spinal fluid were negative. Injections in the guinea pig were positive.

On x-ray examination, no evidence of pulmonary tuberculosis was found, but there were many calcific nodules in the spleen, and a diagnosis of primary tuberculous complex of the spleen was made.

COMMENT

Two of the patients described showed good clinical response to streptomycin therapy, but the prognosis in both cases is still grave.

Case 2 showed some response but continued to have visual disturbances and signs and symptoms of hydrocephalus when he was discharged from the hospital, so that he is now blind even though the disease seems to be temporarily arrested.

Case 5 seems to have improved.

The remaining patients showed little or no response to streptomycin, and this result corresponds well to those mentioned in Feldman's series.

By determining the content of streptomycin in tissues of the various organs at necropsy, Baggenstoss and his associates^{7, 8} have shown that following large doses of streptomycin (10 Gm. intramuscularly), significant amounts were found in the blood (120 μ g per gram), cerebrospinal fluid (15.8 μ g per gram), kidney, spleen, liver, etc. The brain, however, was completely devoid of the drug. Furthermore, pathologic evidence of healing within the miliary tubercles was evident in the lungs, liver, etc., while there was a lack of any signs of regression in the tubercles in the brain.

The fact that streptomycin reaches the cerebrospinal fluid through the blood stream and/or by intrathecal injection may explain the early clinical response occasionally observed in isolated cases. However, the tuberculous process is often initially seeded in the brain as well as in the meninges, and since the process in the meninges often extends into the brain substance, where neither streptomycin is present nor healing evident, the poor prognosis and eventual poor outcome of patients with tuberculous meningitis become apparent. Although streptomycin has given us some hope in the treatment of tuberculous meningitis, much is yet to be desired toward complete recovery from this disease.

In general, the object of treatment is to give large doses of streptomycin and thus maintain a high blood level so that the local concentrations of the drug remain high.

In adults the intramuscular administration of 1.0 Gm. of the drug at six-hour intervals is ordinarily adequate for most infections. This amounts to 4 Gm. per day. Larger doses are sometimes necessary, and up to 8 Gm. may be used if necessary. Infants and children require smaller doses—30 to 75 mg. per pound or 0.25 to 2.0 Gm. daily are adequate.

Intramuscular injection is the parenteral method of choice. In some cases intrathecal administration has been used to supplement the intramuscular route. Intrathecal doses should be smaller, and 25 mg. a day have been reported in infants without serious effect. Injections of more than 50 mg., however, may produce signs of meningeal irritation since there is a chemical irritation giving rise to arachnoiditis.

The use of streptomycin is not without danger and toxic effects. Local reactions are common and consist of pain and induration at the site of injection. This is a minor reaction and can be lessened by giving procaine simultaneously. Constitutional reactions are varied and are more severe. Headache, nausea and vomiting, and flushing of the skin have been reported. These may be due to impurities in the drug. Skin lesions vary from erythematous to hemorrhagic, urticarial to maculopapular. An interesting finding is eosinophilia with or without a skin rash.

The most important reaction is the disturbance of function of the eighth nerve, which probably represents a neurotoxic action of a selective nature. The disturbance is both vestibular and cochlear. Vertigo is prominent, and the Romberg test is positive in most patients. This disorder seems irreversible, but patients soon compensate for the defect by other postural mechanisms so that

symptoms are alleviated after a month or so. Deafness also occurs due to cochlear damage. Tinnitus generally precedes the deafness, which may be temporary or permanent. Cases have been reported in which hearing returned following cessation of therapy, only to become impaired again when streptomycin was reinstituted.

At the present time, there are six additional patients being treated for tuberculous meningitis in this hospital. One has an additional bone involvement and cold abscess and is just about holding his own. The remaining five patients are improving clinically much as in our earlier cases.

SUMMARY

The case histories of nine patients ill with tuberculous meningitis and treated with streptomycin have been reviewed. In two, temporary clinical response was obtained.

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THE IMPORTANCE OF PEDIATRIC AND SURGICAL CARE IN THE PREVENTION OF SELECTIVE SERVICE REJECTIONS

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A RECENT study by Dr. I. G. Greer of five large white orphanages in North Carolina (Presbyterian Orphans' Home, Methodist Children's Home, Methodist Orphanage, Oxford Masonic Orphanage, and Baptist Orphanage) showed that 1,138 men and women who grew up in these institutions were accepted by the armed services and only sixteen or 1.4 per cent were rejected.¹ The national percentage of rejection for white men who had not previously been examined was 36.1. For the same group in North Carolina as a whole the percentage was 44.6.

It is possible that the high North Carolina rejection ratio was due to the fact that the State had the highest rate of volunteers—many youths who believed that they could pass the physical examination did not wait for the draft. As a result, many of the Selective Service registrants in North Carolina were physically unfit. It also is possible that the low percentage of orphanage rejections was partially due to the fact that some orphans with irremediable defects were not accepted by the orphanages and were sent to special hospitals. However, even with this correction the conclusion is inescapable that the good pediatric care, periodic examinations, the correction of remediable defects, and the balanced diets which the orphans received were responsible for their health. The reports from the National Headquarters of the Selective Service System^{2, 3} have therefore been analyzed, in order to determine the conditions and defects which could have been corrected by competent pediatric and surgical care during infancy and childhood so that the incidence of Selective Service rejections could have been reduced.

Musculoskeletal abnormalities were the leading cause of rejection in white registrants, accounting for 8 per cent, and ranked second in Negroes, representing 4.3 per cent. Deformities resulting from rickets are preventable in infants by adequate diets and early administration of cod liver oil. Such deformities as genu varum, valgum, and recurvatum can be corrected by orthopedic surgery. Abnormalities of the spine, which include scoliosis, lordosis, and kyphosis, are often corrected early in life by exercises. Arthritis, ankylosis, and atrophy may be arrested before disabling deformities can result by early definitive treatment. Torticollis and the residuals of osteomyelitis can be corrected by specific orthopedic surgery.

The incidence of hernias was found to be the second cause of rejection in whites (6.3 per cent) and third in Negroes (3.2 per cent). It is well known that some inguinal and femoral hernias in infants disappear spontaneously and may be reduced easily. Surgical treatment results in a good prognosis if the

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operation is deferred until the age of 2 years. Strapping with adhesive tape is usually sufficient for umbilical hernias in infants, although if they are very extensive an operation may be necessary.

Conditions classified as neurological included residuals of poliomyelitis, chorea, enuresis, and epilepsy. This group ranked third in whites and fifth in Negroes as cause for rejection which could have been corrected. Obviously, individuals afflicted by residuals of poliomyelitis cannot be completely rehabilitated by corrective orthopedic surgery, but many can be restored to functional activity. The incidence of poliomyelitis during epidemics can be lowered by delaying elective tonsillectomies and adenoidectomies. Certainly little can be done preventively for congenital and Huntington's chorea. In children, enuresis is often due to poor habit-training. Idiopathic epilepsy, although not preventable, can usually be controlled by proper medication.

Eye defects were the fourth most frequent cause of rejection in whites and eighth in Negroes. Errors of refraction, such as astigmatism, hyperopia, and myopia, require early expert ophthalmic care and refraction. Deformities such as ptosis of the eyelid, ectropion, entropion, dacryocystitis, pterygium, and strabismus can also be corrected by ophthalmologic surgery. Insufficient or poor lighting is responsible for many cases of asthenopia. Prompt consultation by an ophthalmologist after diagnosis will prevent more serious defects.

Conditions of the ears ranked fifth as a cause for rejection in white registrants. Otitis media and complications such as mastoiditis, brain abscesses, and lateral sinus thrombosis have become much less a problem with sulfonamide and penicillin therapy. Children with frequent upper respiratory infections and otitis media can be aided immeasurably by adenoidectomy and tonsillectomy.

Tuberculosis ranked sixth in whites and seventh in Negroes as a preventable cause for rejection. Routine tuberculin tests and x-rays of positive reactors are more valuable aids in the detection of tuberculosis than are physical examinations. The early recognition of active pulmonary tuberculosis and isolation with treatment will reduce the incidence of tuberculosis. The importance of pasteurization for the prevention of milk-borne infections is well recognized. The household use of raw milk, however, by supposedly educated parents is not uncommon.

Other lung conditions in whites ranked seventh as a preventable cause of rejection. The prevention of bronchitis, bronchiectasis, lung abscess, and empyema can be accomplished by the early use of sulfonamides and penicillin, by early and adequate treatment of dental caries, and by the avoidance of nose and throat operations while pyorrhea, stomatitis, or upper respiratory infections are present. The prophylactic use of arsphenamine when foreign bodies are removed from the bronchi may prevent spirochetal abscesses. The early treatment of sinusitis, allergy, and atelectasis, and the removal of diseased tonsils and adenoids will aid in the prevention of lung conditions.

Being underweight or overweight was the eighth cause of rejection in white registrants. Adequate diet is essential for good nutrition. The population at large should be educated in regard to adequate and well-balanced diets. This type of education is now being carried out by various government agencies and life insurance companies through the press, radio, and magazines. Children

after the age of 3 years should be taught to stand, walk, and sit properly. If every child, as early as possible, is given "setting-up" exercises and is frequently instructed in good body mechanics, growth and well-being usually will be satisfactory, and postural deformities, failure to gain weight, and lack of vigor generally will be avoided. Corrective exercises in a gymnasium may be needed for those who have a poor body-mechanics. Such a program should be carried out in the schools.

Conditions of the abdominal viscera ranked ninth in the causes of rejection of white registrants. In this group, chronic appendicitis and peptic ulcer with their complications were frequently found. Peptic ulcers, which are rare in children, usually are controlled by conservative therapy, although surgical treatment may be necessary in those cases that fail to respond. Appendectomy in children is attended with a low mortality rate if performed within twenty-four to thirty-six hours after appearance of the initial symptoms. Since the diagnosis of appendicitis in children is often difficult, all patients with signs and symptoms of acute appendicitis should receive the benefit of the doubt and be operated upon. Older children and adults with recurrent attacks of appendicitis should have their appendices removed.

Syphilis in Negroes accounted for 20.5 per cent of the preventable rejections, being the leading cause in that race. Ignorance, poverty, and indifference are the main factors responsible for this high incidence. Routine serologic tests on all parturient women and on all infants, and recognition of syphilitic stigmata should result in a decrease of congenital syphilis.

The obvious neglect of dental care is evidenced by the high incidence of teeth defects. An adequate vitamin diet, regular brushing of the teeth, and visits to the dentist are essential for healthy teeth. In addition to vitamins, the child's diet should contain at least 1 Gm. each of calcium and phosphorus daily. The deciduous teeth should be preserved in good condition as long as possible since their early loss may be responsible for faulty alignment of the permanent teeth, and caries.

Deformities of the feet ranked sixth in Negroes and tenth in whites. Most types of clubfeet respond well to orthopedic treatment if treated early. *Pes planus* can usually be corrected early by proper foot exercises. Callosity, corns, bunions, and *hallus valgus* can be prevented by instruction as to properly fitting and constructed shoes.

Skin defects were especially prominent in the white registrants. *Acne vulgaris*, if seen early between the ages of 8 to 12 years, during the "blackhead" stage, can be controlled in over 80 per cent of adolescents by keeping the skin dry and rather chapped, and by the use of mild and later stronger soaps and of *lotio alba* of increasing strength. Dietary therapy may be beneficial. Fungus conditions, especially of the feet, are controllable by keeping the feet dry and using fungicidal powder or ointment. The underlying sensitivity producing eczema at present cannot be prevented, but eczematous children should be protected against infections and extreme cold, and should not be given eggs, serum, or vaccines unless absolutely necessary and then only with extreme caution.

Furunculosis can be prevented by cleanliness of the skin and the immediate application of an antiseptic solution to abrasions. Children should be taught that abscesses should not be squeezed. High vitamin diet and injections of autogenous vaccines or staphylococcus toxoid may also be useful. Personal cleanliness is probably the best preventive measure for impetigo, scabies, or pediculosis.

Among the white registrants, nasal defects were very frequent, septal deviation and hypertrophy of the turbinates being commonly found. Unless the obstruction requires immediate attention, it should be corrected surgically in children after the age of 6 years. Nasal polyps should be removed surgically if they are producing symptoms. Sinusitis occurs more frequently in children who are allergic or who have frequent upper respiratory infections, and usually requires radical treatment to prevent bronchiectasis. If the sinusitis is due to allergy, the patient should be desensitized to the offending protein. Occasionally the reverse is true and allergic conditions are caused by chronic sinusitis; the symptoms disappear after the sinuses have been drained.

Throat conditions were among the leading causes of rejection. Of this group, tonsillitis and pharyngitis had the highest rate. Individuals who are more susceptible to tonsillitis and pharyngitis should avoid exposure to people infected with colds, since colds precede more severe infections of the rhinopharynx. If children who have "just a slight cold" were urged to stay home from school and were kept in bed at the onset of illness, recovery would be more rapid and contact cases avoided. Susceptibility to colds would be reduced if the humidity in the home and classroom were increased. Approximately 20 per cent of children after the age of 3 or 4 years should have their tonsils and adenoids removed, especially those who have had repeated respiratory infections with persistent cervical adenopathy, markedly enlarged tonsils with obstructive symptoms, chronic otitis media, rheumatic fever, acute glomerulonephritis (following tonsillitis), and childhood tuberculosis, and those who are diphtheria carriers; at least 50 per cent of this group are benefited. Removal of adenoids is indicated in infants who have nasal obstructions, chronic otitis media, or sinusitis.

Varicoceles, hydroceles, and hematoceles are rare in children. If present in infants, hydrocele usually disappears before the age of 2 years without treatment. Scrotal suspensories, aspiration, or injection may be advisable. Occasionally surgical treatment is required. For the prevention of balanitis, paraphimosis, and phimosis, cleanliness of the penis is essential, and circumcision should be done if the foreskin is redundant or difficult to retract. Chordee should be repaired surgically at the age of 3 years, and plastic surgery for hypospadias and epispadias should be done at 6 to 8 years of age.

Gonorrhea and other venereal diseases were prevalent in Negroes, being the eighth leading cause of rejection. Prevention in adults can be accomplished in great part by proper sex instruction of children, preferably in the home, and by educational measures as carried out in the armed forces.

Last but not least, it is likely that the quiet, regimented life which the orphans had led, in spite or because of its obvious lack of parenteral attention, was an important factor in their low percentage of rejections because 12 per cent of all Selective Service rejections were due to neuropsychiatric disorders.⁴

CONCLUSION

At risk of carefully delineating the obvious, to quote William James, better pediatric and surgical care might have decreased the incidence of Selective Service rejections. An analysis of the reports of Selective Service shows that many of the causes of rejections might have been prevented or corrected during infancy and childhood. Lack of pediatric care is mainly due to ignorance on the part of parents who rarely think in terms of prevention but call for medical aid only when the child is ill.

The purpose of this paper is to emphasize the need for better pediatric care, and to discover why the Selective Service rejection rate of the graduates of the North Carolina orphanages was so much lower (1.4 per cent) than that for the State (44.6 per cent).

Addendum

Dr. Maurice H. Friedman, speaking at the third annual meeting of the National Conference on Rural Health held in Chicago in February, 1948, reported the following conclusions:

1. There was no significant difference in the per cent of rural and urban youth selected for the armed service. Actually the data show more rural white men were accepted for service than urban white men.

2. The percentage of Negroes accepted for service was far less. Over two-thirds of Negro rejections were accounted for by syphilis, educational and mental deficiency, and mental disease.

3. Detailed examination of all recorded defects in Illinois, Indiana, and Iowa shows no significant differences between the rural and urban populations, even though the cream of the farm youth was kept on the farms by priorities and never appeared for examination.

4. This does not entitle us to conclude that the health of the farm youth is as good as the health of the urban youth. On the basis of the Selective Service statistics we cannot draw any inferences as to the health of the farm youth since these statistics are not a reliable guide to the health of a community.

5. Conclusions regarding the medical care of a community cannot be drawn even when the "health" of a community is reliably and accurately measured, for medical care is only one of many factors which determine community health.

6. With respect to many diseases, socioeconomic factors, such as geography, density of population, housing, race, and ethnic or cultural background, are of more importance than the availability of medical care.

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Case Reports

PRECOCIOUS PUBERTY WITHOUT A DEMONSTRABLE TUMOR

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PRECOCIOUS puberty was once thought to be due entirely to a disturbance of one of the endocrine glands and most often to a tumor of one of these glands. Cases have been recorded of sexual precocity caused by granulosa cell tumor of the ovary,¹ adrenal tumor or hyperfunction,² testicular tumors, central nervous system lesions, especially midbrain neoplasms, and more rarely tumors of the pituitary and pineal glands.³

Novak has reported a group of cases of a type of precocious puberty which he says is the most common of all, the constitutional type. The etiology is unknown, but it is postulated to be due to an abnormal genetic factor. It is his opinion that children with constitutional precocity develop a perfectly normal puberal phenomenon at an abnormally early age, skipping the childhood period between infancy and adolescence.

The clinical picture of female children of this group is that of a child who is larger than her chronological age, has varying degrees of development of the secondary sexual characteristics, and has an adult type of reproductive organs with a regular menstrual period. Even ovulation occurs in this group.⁴

It was felt that the following case most probably fits in this category.

CASE REPORT

A. L. K., a 3-year-old Negro girl, was admitted to the Jefferson-Hillman Hospitals on Feb. 6, 1946. The child's mother stated the child's breasts had been abnormally large at birth and had continued to grow slowly, and by the time she was 9 months old they were definitely enlarged. There had never been a discharge from the nipples. Shortly before her first birthday she began to pass some dark brown material per vagina. The material was described as being about the same color and consistency as floor wax. From this time on she began to have such periods regularly every twenty-eight to thirty days. This type of period continued for about one year, and then the character of the flow changed to what the mother described as, "Looks like what I pass during my period." The periods lasted three days, the amount of flow being approximately the same each day. During the periods the mother would put a diaper on the child, and by evening the diaper would be well soiled. On admission the child was having a period, and her panties had eighteen to twenty drops of blood on them, covering most of the bottom of the underwear.

She was the first child, being delivered in this hospital without difficulty. There were no complications in the early postnatal period. She had had none of the childhood diseases and no serious illnesses or operations.

The developmental history was normal.

So far as the mother knew the child was not aware of her condition and exhibited no libido.

Physical Examination.—The blood pressure was 92/54, temperature 99° F., respirations 22, pulse 84.

The child was 43 inches tall and weighed 45 pounds. The general physical development appeared to be that of a child about two to two and a half years older than the patient's stated age. The general body contour was that of post-puberty.

No abnormalities of the head or skull were noted. The eyes and eye grounds were normal. There was slightly more hair on the face than is usual for the age. She had a full complement of deciduous teeth. Nothing of note was found in the examination of the ears, nose, and throat or of the neck.

The breasts were fully developed. There seemed to be slightly less ductal tissue than in an adult breast of the same size. No nipple secretion was noted.

The lungs and heart were not remarkable. The abdomen was flat. No organs or masses were palpated. A large umbilical hernia was present.



Fig. 1.—Three-year-old Negro girl showing sexual precocity. Note absence of pubic hair.

In examining the genitalia, a very slight amount of pubic hair was found. The labia majora and minora were well developed. The introitus easily admitted one finger. Vaginal rugae, typical of those of an adult, were seen. The clitoris was not enlarged. The uterus was enlarged to the size of that of an adult and occupied a posterior position. The right ovary could be felt and measured about 2 by 3 cm.

The extremities were not remarkable, except that the fat distribution and shape were those of adolescence.

Laboratory Data.—The blood picture was within normal limits. Urine Kahn and Mantoux tests were negative. In a twenty-four hour urine sample, 1.5 mg. of ketosteroids and less than 6.6 mouse units of gonadotropic hormone were excreted. These amounts are within normal limits for the age.⁵

Anteroposterior and lateral views of the skull showed no abnormalities. The bone age was found to be that of an 8-year-old. The long bones appeared normal.

The patient had an I.Q. of 85 to 100 and a mental age of $3\frac{1}{2}$ to 4 years.

About ten days after the last menstrual period, a cervical and vaginal smear was made and stained. It was found to contain stratified squamous epithelium, similar to that found in adults showing estrogenic activity.

Twenty-five days after the beginning of the last menstrual period, under general anesthesia, a pelvic examination was done. Findings were essentially the same as on admission. At this time a dilatation and curettage were done. The pathologic report was: "Two to three cubic centimeters of soft, grayish brown endometrial scraping submitted. The endometrium is composed of numerous glands, which are fairly large and dilated in some areas. The epithelium is tall with basally placed nuclei. There are no secretory vacuoles present. The stroma is dense. Impression is that the endometrium is in a proliferative phase."

Since it is known that a very small tumor of the ovary can produce such a picture, and due to the fact that the uterine scrapings did not show ovulation, it was felt that a laparotomy was justified to search for an ovarian tumor.

On March 12, 1946, under ether anesthesia, a low midline incision was made and the pelvis explored. The right ovary was partially resected, removing an old retention cyst. The left ovary was normal except for a few small cysts, which were punctured with a needle. An appendectomy was done and the abdomen closed. The pelvic organs were said to be the size of those of a 15-year-old girl.

The pathologic report on the ovarian tissue was: "The specimen is a portion of an ovary which consists of essentially a thin-walled cyst covered with white tissue. The lumen is empty, and the wall is red. A question of lutein was present at operation; however, nothing suggesting lutein tissue is present in the gross specimen. On microscopic examination, the ovary contains many primordial follicles and one ripening Graafian follicle. There is a small proliferous cyst. Nowhere in the section is there anything suggesting lutein tissue."

The patient made an uneventful recovery. After explaining her condition to the mother, the patient was discharged to the outpatient clinic.

Since then she has been seen twice. She has gained 2 pounds, and her menstrual periods have increased to four days. The amount of flow has also increased. Other attempts to admit the child for endometrial scrapings to look for definite evidence of ovulation have failed since she would not re-enter the hospital.

SUMMARY

A case of precocious puberty has been presented. It is felt that this case probably should be classified as the constitutional type of Novak, although definite proof of ovulation was not obtained.

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URETHRAL BLEEDING IN MEASLES

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A 7-YEAR-OLD girl in the third day of the eruptive stage of rubeola began to bleed from the vulva. The mother applied sanitary pads, three of which had become saturated with blood before the child was examined by a physician. Inspection revealed a large, firm blood clot distending the urethral meatus. Some blood was seen oozing around the clot, and she was able to void around it. The clot was grasped with a forceps and part of it broke off; the remaining portion seemed to be adherent to the urethral wall above. It was not disturbed further, and there was no more bleeding. The appearance of the lesion suggested a bleeding polyp or some type of urethral tumor, which would be a rare lesion in a child this age. One of the country's outstanding urologists happened to pay me a visit at this time, and because the case was unusual he kindly consented to see the patient with me. He, too, thought she probably had a pre-existing lesion in the urethra, and we decided that she should be examined after she recovered from the measles, and if a polyp or tumor was present, it should be treated accordingly. The child was examined two weeks later, and the area was entirely healed. The attack of measles seemed to be very ordinary in other respects and there was no other bleeding.

I have been unable to find a reference regarding bleeding from the urethra in measles, though hemorrhage from the mucous membranes, mouth, nose, and intestinal tract is known to occur.¹ In conversing with pediatricians, I have been unable to find one whose experience has included a patient with such a complication.

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HYPERTROPHIC PYLORIC STENOSIS IN A NEWBORN INFANT

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THIS is a case report of hypertrophic pyloric stenosis in a newborn infant. Symptoms of obstruction of increasing severity developed on the second day of life. The infant was successfully relieved by the Fredet-Rammstedt operation on the fourth day of life. After a difficult postoperative period, growth and development continued in the usual fashion.

CASE REPORT

History.—C. D., a white infant girl, weighing 8 pounds, 3 ounces, was delivered at term of a mother 41 years of age, para iii, on Dec. 12, 1947, after a four-hour labor. Spontaneous cry and respirations were vigorous. The father, 46 years old, and three other children, a son 24 years, a daughter 11 years, and a son 5 years of age, were living and well. The daughter was a feeding problem from birth. It was necessary to give her drops of atropine before each feeding for the first six weeks of life to prevent vomiting.

Clinical Examination.—The infant was seen the morning of Dec. 13, 1947, by the pediatrician on duty, and appeared normal on physical examination. There was no evidence of intracranial injury.

At 12 hours of age, 5 per cent glucose water was offered by mouth every four hours. At 24 hours, ward evaporated milk formula was offered every four hours. On Dec. 14, thirty-six hours after birth, the first afternoon feeding was forcefully ejected through the nose and mouth in projectile fashion fifteen minutes after the end of the nursing period. The infant was again placed on 5 per cent glucose water feedings. These were partially returned with retching, along with thick, viscid mucus. No bile staining occurred. The infant was passing small quantities of urine and meconial stool at four- to six-hour intervals. The left upper quadrant was moderately distended. There was audible borborygmus in the small intestine, and the infant passed flatus during the examination. Digital examination of the rectum was normal. Atropine sulfate solution (1:1,000), increasing from one to three drops, was administered before feedings. Formula was thickened with cereal. Twenty cubic centimeters of isotonic saline were given subcutaneously every three hours.

The child improved and all feedings were partially retained for two days, and then forceful, complete return of feedings began fifteen minutes after they were taken. The weight at this time was 7 pounds, 9 ounces. The evening nurse had reported a small quantity of milk stool in the last meconial bowel movement. Mild icterus neonatorum had developed. There was a high-pitched, agonized cry of pain at frequent intervals. The eyelids were quite edematous. Inspiratory rales could be heard at the right base posteriorly and in the left axilla. The cord had dropped off, leaving a slightly infected, moist stump. The liver was 4 cm. below the costal margin in the midclavicular line. There was marked distention of the left upper quadrant. No waves could be made out. Attempts to palpate a pyloric tumor during nursing and after vomiting were unsuccessful.

Laboratory data: hemoglobin 14.0 Gm., red blood cell count 5.17 million, white blood cell count 14,400 with 53 per cent polymorphonuclears, 36 per cent lymphocytes, 8 per cent myelocytes, 3 per cent eosinophiles. There was no growth in the blood or in catheterized urine cultures. The urinalysis was normal.

The infant was given 20 c.c. of Lipiodol by nipple, and fluoroscoped. The oil encountered difficulty passing the cardiac sphincter but did go through finally

in small squirts. By change of position and abdominal massage, a small drop of oil was milked through a string-sized pyloric canal and moved rapidly into the jejunum. There was a lemon-shaped shadow on the film with a nipple protrusion into the pylorus. The three-hour film demonstrated considerable retention with a little oil in the small intestinal loops (Fig. 1).

Diagnosis.—A diagnosis of pyloric obstruction with stenosis was made, and an exploratory laparotomy was advised.



Fig. 1—Roentgenogram taken preoperatively showing retention of Lipiodol in stomach and nipple-like projection at pylorus

Operative Note.—The infant was taken to the operating room in good condition, and an infusion of 5 per cent glucose in saline was started. Open drop ether anesthesia was administered. A high, vertical, right rectus-splitting incision was made. There was no free fluid in the abdomen. The stomach was moderately dilated, and the pylorus contained a definite lemon yellow tumor approximately 2.0 cm. long, of almost cartilaginous consistency. No other abnormalities were found. The serosa was opened by sharp dissection over the entire length of the tumor, and the underlying muscle was separated to the mucosa. There was slight oozing but no free bleeding. At the completion of the Fredet-Rammstedt procedure, the pyloric mucosa was seen to pout up into the muscular defect, affording relief of the previous obstruction.

Postoperative Clinical Course.—The infant was returned to the ward in good condition with a Wangensteen suction in place and the remainder of 100 c.c. of whole citrated blood run in by slow drip. Suction was discontinued the next day and 5 to 10 c.c. feedings of 5 per cent glucose water were offered by dropper every two hours. During the next two days the infant partially

or completely regurgitated feedings by mouth, usually quite promptly after being fed. On December 19, two days later, the infant was again fluoroscoped and offered 20 c.c. of Lipiodol by nipple. There was marked cardiospasm and some dilatation of the esophagus. This spasm was dilated with a gavage tube. Oil promptly passed on through into the intestinal tract (Fig. 2). Peristalsis and reverse peristalsis from the jejunum on up were extremely active.



Fig. 2.—Postoperative X-ray revealing prompt passage of Lipiodol into small intestine but partial retention in esophagus.

During the next four days, hydration, and urinary output were maintained as indicated with 100 c.c. hypodermoclyses of 5 per cent glucose in distilled water or isotonic saline. The infant was given sodium luminal gr. $\frac{1}{4}$ every six hours by hypodermic injection, and atropine by mouth or by injection to the point of intoxication before each feeding. The nursing staff fed the infant cereal-thickened formula by Breek feeder or gavage. Repeated regurgitation of bile-stained stomach contents continued unabated.

The wound healed clean and well. On December 23, the first normal-sized, soft yellow bowel movement appeared. Thereafter, regular movements continued which were normal in size and consistency. Clyses were discontinued.

The infant developed a temperature of 101° F. by rectum on December 27. Examination revealed a purulent nasal discharge and a slightly infected pharynx. The nose and throat culture grew out *Staphylococcus*, and

Escherichia coli bacteria. Therapy consisted of 10,000 units of penicillin every three hours for three days, by hypodermic injection. Recovery from the respiratory infection was complete.

Atropine and thickened feedings were discontinued on December 30, and the child was placed on an evaporated milk and Karo formula. She was discharged on Jan. 2, 1948, the seventeenth postoperative day, weighing 8 pounds, 7 ounces. The hemoglobin was 16 Gm., the red blood cell count 5.5 million, the white cell count 9,500 with a normal differential. Urinalysis was normal.

The patient was seen in the outpatient clinic Jan. 7, 1948, at which time she weighed 8 pounds, 11 ounces. On February 10, at 9 weeks of age, she weighed 11 pounds, 2 ounces, and the length was 23 inches. There had been no vomiting. The child's development was normal.

DISCUSSION

MacHaffie¹ reported a similar case of an infant girl with hypertrophic pyloric stenosis who was operated on at 34 hours of age. No other report of this condition producing obstruction in the newborn period has been found in the literature. Our patient was operated upon with the thought in mind of relieving a pyloric obstruction due to congenital stenosis, as a pyloric tumor seemed only an academic possibility.

The etiology of hypertrophic pyloric stenosis is not clear. The question arises whether the hypertrophy of the circular smooth muscle sphincter with stenosis precedes or follows pylorospasm. Wallgren,² in careful serial x-ray studies, concluded it was improper to speak of this condition as "congenital." Donovan³ and Ladd and Gross⁴ mention finding the tumor in premature infants and in other infants too early in life for spasm to have caused the hypertrophy. Donovan states there is no correlation between the size of the tumor and the age at operation, and makes the point that the variation in the severity and the time of onset of the symptoms seems to be due to the amount of pylorospasm rather than the size of the tumor.

In our patient, the tumor was congenital. The spasm developed on the second day of life. It was not amenable to medical care. Obstruction was confirmed by x-ray examination. The postoperative course was jeopardized by severe cardiospasm, undoubtedly aggravated by suction and gavage tubes. It is of interest to note that MacHaffie's patient and our own were female infants, the third and fourth pregnancies, respectively, and both showed only a distention of the left upper quadrant, without a wave or tumor demonstrable. The postoperative course in both cases was complicated by continued vomiting for several days. Our patient's sister had a milder but possibly similar condition, relieved by atropine.

SUMMARY

A case of hypertrophic pyloric stenosis with obstruction is reported, which developed on the second day of life and was successfully relieved by operation on the fourth day of life. Attention is called to the report of another case. The infant was female, the fourth child of middle-aged parents, and had a fully developed pyloric tumor with cardiospasm and pylorospasm of marked degree. The infant was discharged on the seventeenth postoperative day, above birth weight, and her subsequent growth and development have been normal in all respects.

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Medical Care

THE MANAGEMENT OF INFANTILE ECZEMA FROM THE PEDIATRIC-DERMATOLOGIC POINT OF VIEW

A THERAPEUTIC CONSIDERATION BASED UPON THE PATHOGENESIS OF THE DERMATOSES

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THE etiology of eczema in infants and children continues to be shrouded in obscurity. With the exception of those few instances in which food allergens and inhalants play important etiological roles and in which their elimination solves the problem, the management of eczema is little different from what it formerly was. In brief, the therapeutics of infantile eczema comprises chiefly the use of certain topical remedies prescribed in answer to the facts observed by the pathologist and clinician and conformable to well-established practices developing from those data. In spite of therapeutic advance, no specific remedy for this dermatosis has yet been discovered.

WHAT IS ECZEMA?

The term eczema has been loosely employed to cover a multitude of dermatologic entities. Infantile eczema is also used as a synonym for atopic dermatitis in infants. "Atopic" denotes a type of allergic hypersensitivity appearing in human beings but not in lower animals, and characterized by a strong hereditary disposition as shown in the eczema-asthma-hay fever complex. Individuals with atopic dermatitis will have a familial history of allergy; antibodies can be demonstrated in their serum by the Prausnitz-Küstner passive transfer test; eosinophilia is frequently present; and they usually respond positively to scratch or intracutaneous tests by an urticarial wheal and flare. In older children and adults true atopic dermatitis is known by a variety of other names: lichen simplex chronicus (Vidal) or neurodermatitis disseminata, the late "exudative eczematoid" of Rost, the prurigo diathesique of Brocq, and the prurigo of Besnier.

Eczema venenatum or dermatitis venenata is a contact dermatitis and is caused by many extrinsic factors including contact with chemicals, plants, and topical medications. Eczema intertriginosum (intertriginous eczema, eczema intertrigo) is characterized by hyperemia. This condition is known as chafing and is frequently seen in the groin and axillae and beneath the breasts in women. Finally we might mention "mycotic" or "nummular" eczema.

To the dermatologist, atopic dermatitis is a definite entity comprising certain well-defined changes in the histopathologic pattern of the skin. The exact description of this pathogenesis is the best definition of the dermatosis.

PATHOGENESIS OF ATOPIC DERMATITIS

Although from a practical point of view there exist no sharp lines demarcating the various phases of eczema one from another, it is perhaps best to discuss the various manifestations seriatim in order to understand clearly the pathologic changes that take place in the corium and in the epidermis.

All eczemas begin as an erythema. The shock organ in atopic eczema is located in the superficial blood vessels (the smaller capillaries and the arterioles) in the upper cutis. It is at that point in the dermatologic network that the allergen (irritant) exerts its damaging influence and so sets in motion a cycle of changes which follow each other in ordered sequence. Histologically these changes occur for the most part in the epidermis, but the corium shares in them, too. There are several ways in which the highly sensitized skin reacts to the allergenic agent. But first, for understanding them, it must be realized that in atopic eczema the skin is different from normal integument in that it is predisposed from the time of the infant's birth to react in a peculiar manner. A large percentage of the parents of eczematous infants, upon being questioned as to the existence of an allergy either among the members of the immediate family or among closely related persons, admit the existence of the condition denominated by Stokes as "the asthma-hay fever-angioneurotic complex." In some studies a positive family history of allergy in as high as 40 to 60 per cent of cases has been obtained. Some children may become sensitized by allergens during their intrauterine life or during nursing. Ratner and others have demonstrated that such sensitization actually does take place through the placenta and through breast milk. Once an infant has become so sensitized, he will always react to the presence of the particular allergen by a regular train of symptoms and signs whenever he comes into contact with it.

The clinical picture of eczema is well known to all pediatricians. After the initial stage of erythema, there follow, as stages in the dermatosis, edema, vesiculation, exudation, and crusting. In favorable cases, healing of the lesions is preceded by scale formation. Various stages of the eczematous condition are often present together. Relapses are frequently seen even when improvement has progressed to the healing stage; even then late edema and oozing may recur. In spite of these irregularities, a diagrammatic representation of the progressive stages of eczema has its use (see Fig. 1).

The histologic picture of eczema in older children and adults is similar to that in infants, except that in very young infants the stratum corneum is thin so that there is lacking the resistance to the edematous fluid furnished by the strongly functioning corneal layer of the older person, with the result that vesiculation and bullous lesions occur much more frequently.

Soon after the allergenic agent has exerted its harmful effect upon the superficial blood vessels of the upper corium, the capillaries enlarge and fill with blood (erythema). The simple inflammatory exudate that surrounds these vessels (defense mechanism) consists of small round cells (small lymphocytes) and wandering connective tissue cells (histiocytes). After the primary insult to the vessels, an outpouring of serum takes place sufficient to invade the

epidermis. Clinically this constitutes the stage of edema. Histologically the edema is of the interstitial type—that is, the prickle cells are not themselves particularly “water-logged” but the interstices of the cells, especially the spaces between the prickle cells, those little “bridges” connecting one prickle cell with another, become the chief site of the edematous change. Varying degrees of edema, dependent upon the mildness or severity of the eczema, can be seen. Thus, in comparatively mild cases the contour of the epidermis is fairly well retained, and its staining property is only slightly affected. On the other hand, in moderately severe or severe cases of eczema, the prickle cells and their staining property are altered (light staining). This alteration, called spongiosis, may lead to the rupture of the prickles. When, in turn, these ruptures become confluent, the result is a vesicle or a series of vesicles. Increased serum to the epidermis means increased nourishment, and the result is the hypertrophy of the prickle cell layer, an acanthosis. Happily the pathologic process in eczema is reversible, so that under conditions of adequate therapy the edema may be made to subside, with restoration of the normal skin following in course. To avoid deep scratching and infection I restrict the motion of the hands by splints and other similar devices.

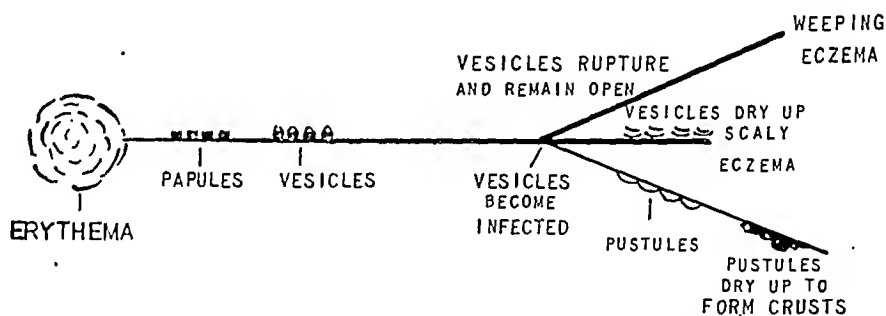


Fig. 1.—Schematic representation of the stages of eczema. (After MacKenna, R. M. D., *Diseases of the Skin*, ed. 4, London, 1937, Bailliere, Tindall & Cox.)

CLASSIFICATION

There are many classifications of eczema in infants and children, several of which are confusing. Perhaps the classification of Sulzberger is best from a combined pediatric and dermatologic practical viewpoint. Sulzberger¹ points out that “Proper classification is important since it determines the therapeutic approach, the prognosis and the proper prophylactic measures.”

I have proposed the following classification of eczema in infants and children, which seems of practical usefulness inasmuch as it indicates the distribution of the lesions under the atopic type.

Atopic Dermatitis (Infants Under 2 Years)*

1. The usual areas: Mostly the antecubital and popliteal regions, both sides of the face, and forehead. A single area may be involved or all three regions

*This type of eczema may be preceded by the seborrheic variety.

may be affected at the same time. This disseminated variety is similar to the *lichen chronicus simplex circumscripatus* of Vidal (circumscribed neurodermatitis) in the classification given by Sulzberger. (See Fig. 2.)

2. The inverse type: The lesions occur upon the extensor surfaces of the elbows and the adjoining surfaces of the skin. The extensors of the thighs and legs are similarly affected. The face may share in the process. (See Fig. 3.)

3. The combined types: Any part of the body may be involved: i.e., the antecubital and popliteal areas with indurated, and lichenified plaques upon the face, chest, buttocks, and elsewhere. This variety of eczema is synonymous with the *lichen chronicus disseminatus* of Vidal and is the type designated as atopic dermatitis by Coca and Sulzberger. (See Fig. 3.)



Fig. 2.—The usual type of atopic dermatitis male infant aged 7 months. Note the sharply demarcated and infiltrated plaques upon both cheeks, which consist of erythema, papules and papulovesicles. Many of the latter lesions have been denuded due to scratching. A number of discrete papules and scratch marks are also seen upon the chin. Similar lesions were demonstrable upon the antecubital and popliteal areas. The patient represents the so-called "wet stage"; considerable "oozing" of the lesions was present at this time. A positive history of bronchial asthma was elicited in the father. The mother has hay fever. (Courtesy of the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, New York.)

THERAPEUTIC INDICATIONS

1. *Rest*.—Physiologic rest is always important for the welfare of infants, but it is even more important for the infant victims of eczema because of their greater losses of energy owing to restlessness, constant crying, and refusal of nourishment. It may be achieved by several means—mechanical, by splinting and other devices, and medicinal, both topical and internal.

Among topical remedies, the colloidal bath in the form of starch, oatmeal, or bran bath is valuable since it serves to allay acute erythema and itching. Accordingly, because of gratifying results, I have made it a rule to instruct mothers in the routine of the starch bath in all cases of eczema. For a proper preparation, the corn starch (Argo or Linet, which are already hydrolyzed, will serve)

should be mixed with water and stirred with a spoon or a wooden stick until the mixture is milky white; and then added to the bathtub of water. Ordinary starch should be prepared as just described and then transferred to a pot over low heat and stirred until it assumes the appearance of ground glass. Then after the paste has cooled, a portion of it is to be applied gently to the infant's skin while the remainder is to be added to a tub of water in which the infant is to be immersed. There the child may remain for five minutes, provided that the room is sufficiently warm. Then the skin may be gently wiped and patted and dried with a soft towel, but under no circumstances must it be rubbed. Such a bath may be employed every day or every second day in cool weather, several times a day in warm weather. To finish off, a fine tale (unseented) may be used to dust the skin. Talcum powder containing zinc stearate should be avoided.



FIG. 3.—Atopic dermatitis. The so-called "combined type." The patient is a boy aged 5½ years and shows in addition to lichenification, induration, denuded papules and crusts upon the usual areas (face, neck, antecubital and popliteal regions). Similar lesions upon the extensors of the upper and lower extremities, representing the "inverse type" of atopic dermatitis. Duration one year. (Atopic dermatitis may involve any part of the body.) A positive history of allergy was obtained in the father. (Courtesy of the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, New York.)

A kaolin bath is soothing to a highly inflamed skin. Kaolin (*Kaolinum*, N.F.) is a native hydrated aluminum silicate, powdered and freed from gritty particles by elutriation. It is closely related to bentonite and is employed in pharmacy as a distributing and filtering medium. When added to warm water in the proportion of ¼ pound to the bathinette of water (¼ pound to 10 gallons of water) it serves as a useful soothing remedy.

Sedatives are certainly indicated at any stage, and the oral barbiturates are the best. I seldom prescribe less than 0.016 Gm. (gr. $\frac{1}{4}$) of phenobarbital sodium (soluble phenobarbital) for very young infants and frequently as much as 0.03 Gm. (Gr. $\frac{1}{2}$) for somewhat older infants, to be given every three or four hours to produce rest. I have never seen untoward effects from the use of barbiturates when given in the manner described. On the other hand, the opiates should never be employed because by the use of them the pruritus is increased and because they are habit forming.

2. *Removal of the Offending Allergen.*—Although removal of the offending allergen remains the ideal method of achieving the therapeutic result, experience has convinced most pediatricians that for the vast majority of patients that method of approach is a waste of time, money, and effort. The scratch test is inconstant in its result. In fact, trial of foodstuffs suspected as offenders has been more successful than the skin test. I believe that more can be learned concerning the allergen from a careful history than from an occasional positive scratch test. After one year of age foods come to play a minor, certainly a less significant, role in atopic dermatitis. Regarding food allergens, Sulzberger¹ states: "The approach through the history, the close observations of the effects of elimination and re-exposure to certain foods, and the constant awareness that a certain few foods are notorious offenders will prove to be more successful, as a rule, than reliance on the results of hundreds of cutaneous tests. For although results of cutaneous tests are, in infantile eczema, often without clinical significance, even accompanied by specific reagins, conversely, substances that fail to elicit cutaneous reactions may nevertheless sometimes be factors in the production of the eruption."

When food proteins, such as cow's milk, egg, and wheat, have been found definitely to be responsible for atopic dermatitis, then, of course, these should be eliminated and replaced in the diet by equally important but nonallergenic foods. Fortunately, there is a large number of such substitutional foods upon the market, among them goat's milk, whole and evaporated, evaporated cow's milk, Mull-Soy, Sobee, and hypoallergic milks.

3. *Maintenance of Adequate Nutrition.*—The discussion of diet suggests the necessity of at least a reference to the safeguarding of the patient's nutrition. I am convinced that it is unwise to treat an infant suffering from an eczema in such a way as to endanger by a strict curtailment of foods his general health to the point of an impending acidosis and possible loss of weight. No treatment, no matter how effective from the dermatologic therapeutic point of view, is justified if the health and nutrition of the patient are actually endangered by it.

4. *The Use and Abuse of Therapeutic Topical Remedies.*—One of the reasons why the pediatrician fails to obtain improvement in the atopic eczematous infant or child is that remedial agents are too often prescribed without a clear-cut indication for their use and without regard to the stage of the eczema. The key to success in the management of dermatoses in infancy or childhood, whether they be eczemas or not, is comprehended in the formula: *Conservatism and*

simplicity in topical remedies employed. A considerable part of the dermatologist's practice consists in treating patients whose skin has been traumatized by the injudicious use of local remedies often prescribed by the general practitioner. This unhappy state of affairs can be attributed to a large extent to the many proprietary preparations high-pressured to the physician. Analyzing the composition of many of these proprietary ointments and lotions advertised for use in eczema, one is amazed at the strength of ingredients dangerous when applied to adults and even more so, of course, to infants and children. Good dermatology like all good therapeutics is an art. The skilled dermatologist is one who has not only a sound knowledge of the composition of the remedies he prescribes but of their correct use, including (of equal importance) the knowledge when not to use them at all. The mere ordering of a useful remedy indicated in the course of an atopic dermatitis is not sufficient; further specific instructions must be given the parent as to how to apply the agent and especially the proper application of bandages.

5. *The Use of Soap and Water.*—I am not convinced that soap and water are irritants to a normal skin although I am convinced that they are bad detergents for a "sick" skin; and for this reason I feel together with most dermatologists that the use of ordinary soap and water are definitely contraindicated as cleansing agents in atopic dermatitis. The free alkali frequently sets up a dermatitis that is especially noticeable in the diaper area. Of course, cleansing the skin is important. The constant application of greasy ointments to the lesions causes the body to give forth a disagreeable odor and also serves to irritate the skin still further. When the ordinary starch bath fails to remove the ointments and other debris (as it seldom does), then one of the newer soaps, the so-called "sulfonated" soaps, may be used to advantage. Sulfonated castor oil (N.F.) may also be used. Bland, nonirritating oils, such as warm olive oil and sweet almond oil, are excellent lubricants. However, several oils popular with mothers, containing hydroxyquinoline, are skin-sensitizers and as such are best left alone.

6. *Restriction of Motion.*—The use of handkeriffs, elbow splints, and other devices to prevent scratching seems to be good therapy, contrary to the opposing opinion of some dermatologists, a considerable number of pediatricians, and sometimes mothers. It should be remembered that in atopic eczema the skin is already the seat of a dermatitis—i.e., it is acutely inflamed. Accordingly, in my opinion nothing could be more absurd than to permit an eczematous baby to scratch because of itching. To do so, means to let him inflict wounds upon the already damaged skin. Furthermore the constant presence upon the skin of streptococci and staphylococci may result upon scratching in a pyoderma often rebellious to therapy. Certainly such a complication is to be avoided. I am not convinced that restriction of motion in infants will necessarily produce ties.² I know, to the contrary, that I have been splinting infants for over a quarter of a century without in a single instance finding the practice harmful in any way. Cutting the nails short does not prevent injury, for rubbing the skin with the hand and so traumatizing it is equally bad. Accordingly, I unequivocally endorse the use of splints.

7. *Environmental Change.*—The management of the eczematous infant or child is by no means a simple or easy task. There is a certain percentage of infants who disappointingly fail to respond to the best management. In desperation the parents have gone on to consult perhaps a half dozen dermatologists without securing improvement for their child. In these recalcitrant eczemas when orthodox therapy has been given a fair trial and failed, the effect of another environment should be tried. An extended stay at the seashore with indulgence in ocean bathing and basking in the sun will frequently produce remarkable improvement. During cold seasons when the seashore in northern climates becomes impossible, the same plan may be carried out upon a warmer coast. Although I am not enthusiastic about transferring an eczematous infant to a hospital, very often the mere change from home to the new atmosphere of the hospital will be sufficient to produce improvement.

MANAGEMENT

The aim in management of atopic dermatitis is to restore to an equilibrium the physiobiologic mechanism of the body. In general, there are two different methods of handling the atopic eczematous infant or child although, of course, both aim at the same object—namely, the restoration of a “sick” skin to a state of health. The first of these, the pediatric approach, tends to emphasize dietetic factors of causation and to minimize the usefulness of the management of the dermatosis. On the other hand, the second approach, the dermatologic, tends naturally in terms of its practitioners’ training, to direct its attention mostly to topical remedies and to ignore the etiological role of food allergens in the disturbances of some infants. (Certainly the role of the allergens is not as important as was formerly believed.) Each of these methods has its place, but the best care for the infant suffering from atopic dermatitis calls for the application of both in combination, with the pediatrician and the dermatologist both making their contributions from their respective specialties. Improvement and ultimate cure depend, in the end, not upon the utility of any single measure or device but upon the joint effort of both specialties. In the meantime any agent that can help to give the patient comfort and rest from itching and prevent recurrence is worth while, be it physical, mechanical, chemical, or galenic, whether a topical remedy, bath, sedation, or the elimination of a food allergen. (See Table I.)

The First Stage.—Examination of the corium and the epidermis under the microscope (see Figs. 4, 5, and 6) shows the tissue laden with fluid. This edema characterizes the process in the “wet stage”; it is a true “water-logging” of the cells of the epidermis and corium. Close examination shows that the edema is not only within individual cells (parenchymatous) but is between cells, in the interstices of the epidermis (interstitial). Edematous tissue stains badly (hematoxylin-eosin), appearing much lighter than normal tissue. The capillaries are dilated, and their endothelial cells are swollen.

At this stage the most important therapeutic indication is the ridding of the water-logged tissues of their fluid content. This draining away of fluid can

TABLE I. SYNOPSIS OF MANAGEMENT OF ATOPIC DERMATITIS

	FIRST STAGE (ACUTE)	SECOND STAGE (SUBACUTE)	THIRD STAGE (CHRONIC)
Pathologic picture of the skin (Simplified)	Edema (spongiosis to vesicles in epidermis). Dilated blood vessels and edema in upper cutis. Inflammatory infiltration in upper cutis	Edematous stage less pronounced than first stage although considerable fluid may still be present in the epidermis	Parakeratosis; acanthosis. Most of the edema has disappeared from the epidermis
Clinical appearance of the skin	Erythema, vesicles, papules, papulovesicles, oozing, crusting	All lesions as seen in first stage, although acuteness of condition is definitely less marked	Indurated, lichenified plaques, scales, scratch marks
Therapeutic indication	Drainage of edematous tissue	Drainage if still necessary. Mild astringent and soothing agents to absorb residue of exudate	Stimulation to restore skin to normal state
Type of treatment*	Continuous wet dressings	Wet dressings if still necessary. Pastes to absorb remaining exudate	Stimulants. Mild counterirritants
Therapeutic remedies	Boric acid (2%); Burow's solution (1 part to 30 parts of water); silver nitrate ($\frac{1}{8}$ to $\frac{1}{4}$ %); potassium permanganate (1 part to 10,000 parts of water or 1 part to 30,000 parts of water); infusion of chamomile tea†	Lassar's simple zinc paste (without salicylic acid) with added medicaments (see below); shake lotions (evaporating) containing zinc oxide, or magnesium carbonate, talc, in various combinations. Zinc oil‡	The tars, 1 to 10%; ichthammol, 3 to 6%; tar ointment, N.F., 25 to 50%; crude coal tar, 6% or full strength; naftalan, 1 to 10% in ointment or lotion. Salicylic acid 3 to 10%, added if necessary as keratolytic

*Antipruritics may be indicated at any time during the course of eczema. Among such remedies may be mentioned phenol, $\frac{1}{4}$ per cent, and menthol $\frac{1}{10}$ to $\frac{1}{4}$ per cent, alone or in combination for their synergistic effect; and benzocaine, 1 to 5 per cent. All of the tars possess antipruritic property. Roentgen rays (36 R.) may be given by the dermatologist at weekly intervals for four doses for their antipruritic effect. The antipruritic effects of a 2 per cent ointment of Pyribenzamine are as yet not definitely established. It should be pointed out that benzocaine has a high sensitizing index and should be used cautiously.

†Chamomile is official in the National Formulary, ed. 8, under the title *Matricaria*. The use of chamomile tea as a wet dressing for the acute and subacute stages of eczema was first brought to my attention by Dr. Max Jessner of the Skin and Cancer Unit, New York. Infusions of chamomile flowers as a wet dressing are particularly useful when continuous wet dressings are indicated and when other topical wet dressings are poorly tolerated by the patient. Chamomile tea may be prepared by pouring one quart (1,000 c.c.) of hot water upon four heaping teaspoonfuls of the chamomile flowers, contained in a suitable receptacle; the latter should then be covered for a period of approximately ten minutes. The infusion is then strained through several layers of muslin, allowed to cool and applied in the form of a wet dressing. Prepared in the manner described, the infusion has a light pink color.

‡Zinc oil consists of 40 parts of zinc oxide, to which are added 60 parts of olive oil (0.0.0.). This preparation should be dispensed in a wide-mouth bottle.

be accomplished by wet dressings applied to the lesions. I prefer either dressings of solution of boric acid or of Burow's solution, with boric acid as the favorite because it is always available, inexpensive, and quickly prepared. It should be used as a 2 per cent solution. (The saturated solution, 4 per cent, is unsatisfactory because it cakes and so interferes with proper drainage.) Burow's solution should be diluted one part in thirty for infants, one part in twenty for children. Where edema is complicated by secondary infection, the use of potassium permanganate in concentrations of 1:10,000 or in baths, of 1:20,000, is serviceable. But of all topical remedies employed as wet dressings, chamomile tea is by far the best. Wet dressings should be applied at room

temperature and kept continuously wet. Several layers of gauze (not cotton) should be used to soak up the solution. The compresses should be employed for a period of twenty-four hours at least and frequently for as long as seventy-two hours although rarely for longer than that period.*

Representative Prescriptions

- 1—R Potassium Permanganate Tablets, N F. 0.3 Gm.
Mitte Tales No XII
Sig Thoroughly dissolve one tablet to three quarts of
water. Continuous wet apphection.



Fig 4

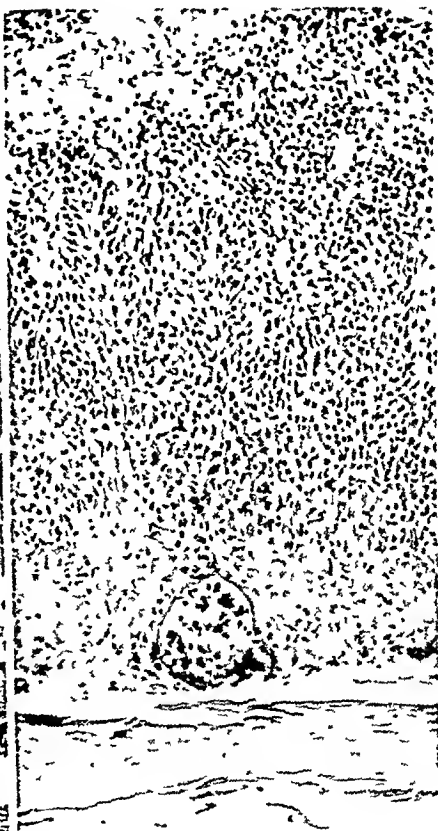


Fig 5

Fig 4—Acute eczema. A marked cellular reaction is seen about the vessels of the upper cutis in the papillary bodies and accompanying the edema into the epidermis (exocytosis). The infiltrate is of the banal type and composed mostly of small round cells. As a result of the severe edema the epidermis is poorly stained and a vesicle has been formed in the upper epidermis. Magnification 192.5 X.

Fig 5—Acute eczema. A marked parenchymatous and interstitial edema is evident in the epidermis. The basal cell margin has been washed out. The cells are large and swollen. The excessive fluid has forced the cells apart (spongiosis). Rupture of many of the intercellular bridges has caused small holes and one vesicle to form within the epidermis. Small round cells which have accompanied the edema from the underlying cutis are visible between the epidermal cells. Magnification 498 X.

*Many dermatologists prefer to cover the gauze employed as a wet dressing with some kind of impermeable dressing, such as wax paper, gutta percha tissue, or oiled silk. Under such arrangement the wet dressing should be renewed every three or four hours.

- 2.—R Aluminum Acetate Solution, N.F.*

1,000 c.c.
- Sig. Add two tablespoonfuls to one quart of water.

Continuous wet application.
- 3.—R Solution of Silver Nitrate

$\frac{1}{8}$ to $\frac{1}{4}\%$
- Sig. For use as wet dressings.

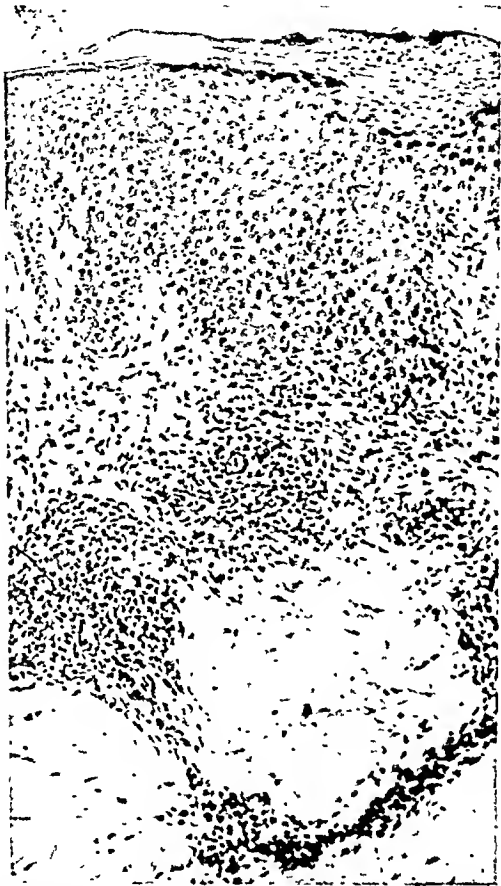


Fig. 6.—Acute eczema. The edematous change in the epiderm^{is} the poor staining quality (lighter color) especially noted in the cent^{er} is a washing out of the basal cell layer of the epidermis. The largely focal i.e., it is centered around the blood vessels in the u^{nder} 192.5 X.

The Second Stage.—The second stage may properly be called the subacute stage; and while there intervenes no clear division histologically between this stage and the first nor between this and the third, certain clinical manifestations warrant its theoretical classification. It is well to remember that the pediatrician dealing with eczema is treating an acute-chronic dermatosis, which runs a varying course, now better, now worse. Indeed, most eczemas are prolonged,

*Domeboro Tablets (Dome) are a convenient means of preparing Burow's solution; the chief advantage over the official solution is that the solution may be prepared extemporaneously. One tablet added to one-half pint of water yields a 1:10 Burow's solution. This solution should be diluted one or two times for infants and children.

and acute exacerbations are by no means uncommon. Where then does the acute process end and the subacute process begin? Clinically one can be reasonably certain that the acute inflammatory process is over when the lesions are no longer "wet"—that is, when oozing has for the most part ceased and the acute erythema has subsided. Histologically it is by no means possible to divide the subacute process from the acute process because the edema remains evident even long after the acute process has run its course. However, progress can be measured in the epidermis by manifestations that should be less severe than in the first stage.



Fig. 7.—Chronic eczema. The following characteristics are illustrated: (1) Interstitial and parenchymatous edema, indicated by poorly staining areas in the epidermis; (2) acanthosis (hypertrophy) of the epidermis; (3) disorganization of the stratum granulosum; (4) increase of the stratum corneum (partly), with retention of nuclei within the horny scale (parakeratosis); (5) subsidence of the acute diffuse inflammatory reaction, which has been replaced by a moderate cellular infiltration (small round and wandering tissue cells) about the vessels of the upper cutis and the capillaries of the papillary bodies. Magnification 125 X.

Itching should be less intense in the second stage although still persistent. Rational treatment will consist of aid to nature in removing inflammation and edema which remain in the epidermis. At this juncture pastes have a particular usefulness, prescribed either alone or in combination with one of the milder tars. It should be remembered that at this stage drainage is still going on through the epidermis although not to the extent that it occurred during the first stage. Accordingly the therapist must bear in mind not to thwart nature in her act of ridding the epidermis of the residual fluid by the application of ointments. Pastes too, when applied, should be spread thinly upon the gauze so that the gauze may still absorb the edematous fluid as it seeps through the

skin. For that reason some dermatologists prefer "shake lotions" to pastes at this point. There is no contraindication to the use of antipruritics if such are called for, or to the use of a mild antiseptic and germicide, which may be added to the paste or the "shake lotion," as the case may be.

Representative Prescriptions

The following prescriptions are suggested for ordering pastes and "shake lotions" during the interim of the acute and chronic stages of eczema:

4.—Basic Formula for a Paste:*

R Zinc Oxide	25 Gm.
Starch	25 Gm.
White Petrolatum	50 Gm.
Misce et fiat pasta.	

Sig. Apply upon gauze or lint twice daily; bandage.

5.—R Menthol	$\frac{1}{10}\%$
Coal Tar†	2%
Zinc Oxide Paste, N.F.	60 Gm.
Misce et fiat pasta.	

Sig. Apply upon gauze or lint twice daily; bandage.

6.—Basic Formula for a "Shake Lotion":

R Zinc Oxide	15.0-20.0
Talc	15.0-20.0
Glycerin	20.0
Distilled Water or Alcohol (30%) q.s. ad	100.0
Misce et fiat lotio.	

Sig. Paint on parts three times daily. Shake well before applying.)

7.—R Ichthammol	2.0
Coal Tar Solution, N.F.	3.0
Zinc Oxide	15.0-20.0
Talc	15.0-20.0
Glycerin	20.0
Distilled Water or Alcohol (30%) q.s. ad	100.0
Misce et fiat lotio.	

Sig. Paint on parts three times daily. (Shake well before applying.)

The seventh prescription contains in addition to the ingredients of the basic lotion, ichthammol (ichthyol) and solution of coal tar, which serve as a mild antiphlogistic and antipruritic. The glycerin (which is really a trihydroxy-alcohol) also helps to suspend more equally the ichthammol and other ingredients. It is permissible to add $\frac{1}{10}$ per cent menthol or $\frac{1}{4}$ per cent phenol, or both, for synergistic effect when additional antipruritic effect is desired.

The Third Stage.—Last to be discussed is the so-called chronic stage of atopic dermatitis. This stage, in which the lesions consist of indurated,

*This prescription is the official Lassar's paste of the National Formulary, appearing there (ed 8) under the title *Pasta Zinc Oxidi*.

†The strength of the crude coal tar may gradually be increased to 6 per cent.

lichenified plaques seen particularly over the antecubital and popliteal areas, is well known to pediatricians. Not infrequently these lesions are superimposed by the secondary infection. Formerly this type of dermatosis was known as squamous eczema. Histologically it is characterized by an acanthosis and interstitial and parenchymatous edema, an increase in the horny layer (parakeratosis), and a moderate cellular infiltration which surrounds the vessels of the upper cutis and the superficial capillaries of the papillary bodies (see Fig. 7).

During the chronic stage of eczema the employment of such measures as will alter the status of the skin and return it to a normal state is indicated. Agents for this purpose are regarded as of the nature of keratolytics and local skin stimulants—that is to say, as remedies that operate in a physiomechanical fashion. Some believe that the improvement following the use of these remedies and devices results from the production of a hyperemia of the skin, which, in turn, summons up the immunologic response of the skin. Older dermatologists produced the effect by the use of the popular flaxseed poultice or by the local application of a 12 per cent salicylic acid ointment, the ointment being allowed to remain upon the lesions for a period of five to ten minutes. Today dermatologists prescribe ointments and lotions containing a tar, to produce the therapeutic effect. Generalized exposure with suberythema doses of ultraviolet light from a mercury vapor quartz lamp as an adjunct to local therapy is advantageous and is prescribed routinely in all infants and children.

Antipruritics may be added, and when called for they should be ordered in mild concentrations. Any of the following antipruritics, either alone or in combination, may be added to the previously given prescriptions:

Phenol	$\frac{1}{2}$ to 2 per cent
Menthol	$\frac{1}{10}$ to $\frac{1}{4}$ per cent
Ichthammol	2 to 5 per cent
Solution of Coal Tar	3 to 5 per cent

Among the tars, I prefer the following, which I have used with gratifying results:

Ichthammol—2 to 6 per cent in zinc ointment or in Lassar's paste.

Crude Coal Tar—3 to 6 per cent in Lassar's paste.

Pine Tar—in the form of the official pine tar ointment in 25 per cent strength for smaller infants and 50 per cent for older infants and children, in a zinc oxide ointment base.

Solution of Coal Tar—5 to 10 per cent in a simple shake lotion.

I have obtained equally good results from coal tars and wood tars. However, my remedy of choice in prewar days (it has since been unobtainable) was naftalan.* I used it in the proportion of 6 per cent, which I gradually increased to 10 per cent, in simple Lassar's paste. The results from its use were most gratifying, indeed, unequalled by those obtained from the use of any similar

*Naftalan, naphthalan (Stieve). The original Russian product was distributed by Ft. Dearborn Drug & Chemical Co., Inc., 126 West Main Street, Louisville, Ky.

R Naftalen (Donner) 7.2—12.0
Zinc Oxide Paste, N.F. 120.0—120.0

Misce et fnt pasta.
Sig. Constant application to the skin.

preparation. I have since substituted the Naftalen (Donner) in its place but cannot say that it is therapeutically as effective as was the original product.

Crude coal tar is employed in 3 per cent strength in the familiar zinc oxide-starch-petrolatum base, and gradually the strength is increased to 6 per cent. It is applied interruptedly, night and day. If the lesions are upon the face, a mask may be useful in keeping the ointment in place. Crude coal tar may also be used as a paint in full strength.^{3†}

It is best to renew the ointments constantly, removing the old ointment before each new application by means of a bland, nonirritating oil such as warm olive oil or sweet almond oil. The pine tar ointment previously mentioned is particularly useful in young infants with atopic dermatitis. Since pine tar ointment, U.S.P., contains wool fat, it should not be prescribed for infants or children who are allergic to wool. For them, ordinary petrolatum and not cholesterinized petrolatum should serve as the ointment base. Ellis⁴ has recently shown that patients who were sensitive to ointment bases and proprietary preparations containing cholesterol as well as wool fat were frequently sensitive to such pharmaceutical bases because of the cholesterol contained in such remedies.

Representative Prescriptions

8.—R	Coal Tar	30.0
	Sig. Paint upon the skin. When dry, apply unscented, purified talc. Bandage.	
9.—R	Pine Tar Ointment, U.S.P.	8.0-30.0
	Zinc Oxide Ointment	60.0
	Misce et fiat unguentum.	
	Sig. Constant application.	
10.—R	Ichthammol	1.8-3.6
	Zinc Oxide Ointment q.s. ad	60.0
	Sig. Constant application.	
11.—R	Coal Tar	7.2-12.0
	Zinc Oxide Paste, N.F.	120.0-120.0
	Misce et fiat pasta.	
	Sig. Constant application.	

Another prescription which has been frequently used in recalcitrant cases of infantile eczema, especially of the face, and in eczema of younger children is a modified Wilkinson's ointment, employed by S. Jessner under the name of "Pasta Nigra." The paste contains the following ingredients:

12.—R	Precipitated sulfur	10.0
	Medicinal Soft Soap, N.F.	20.0
	Zinc Oxide Paste, N.F.	20.0
	Coal Tar or Juniper Tar, U.S.P.	10.0

[†]Sulzberger¹ writes as follows concerning the use of crude coal tar in the treatment of infantile eczema: "I have found direct application of undiluted tar, painted directly on the face—a thick layer covered with purified talc—to be one of the very best of all methods of treatment. This method of application has in my hands been not only more effective but also, on the whole, less likely to irritate than any other remedy. The tar should be left on from one to three days, and then a face mask with yellow or borated petrolatum should be applied for twenty-four hours. The tar painting should then be repeated, the layer to be left on for another two, three or four days, again followed by a day of lubrication. This procedure can be repeated several times more if necessary. (The baby should not be exposed to sunlight when tars in any form or other sensitizing agents are used.)"

To prepare this ointment properly the first three ingredients should be mixed *secundum artem*; then the crude coal tar or oil of cade should be incorporated thoroughly until a smooth, homogeneous ointment results.

According to S. Jessner, the ointment is applied to the face by means of a mask, or if applied to other parts of the body, properly bandaged. After twenty-four to forty-eight hours one finds the skin mostly dry and the paste adherent. Without cleansing the skin the paste is reapplied over the former application and continued in this manner until the skin exfoliates. Then after the skin has peeled, it is cleansed every two or three days by the gentle application of purified benzine or by means of warm olive oil. The paste is then reapplied. After another two or three days the paste is reduced in strength by adding additional amounts of zinc oxide paste; after the first two weeks equal parts of the *pasta nigra* and zinc oxide paste are used. A week later the paste is reduced still further to one fourth the original amount of the *pasta nigra*, to which is added three times the original amount of zinc oxide paste. The procedure as outlined above must be continued until the skin has returned to a nearly normal state and until the itching has disappeared. As a final step to complete the therapy, 2 per cent ichthammol in zinc paste should be ordered. Of course, frequent urinalyses should be carried out while the patient is receiving the topical applications of the modified Wilkinson ointment. I have employed the preparation in the manner described and can praise its therapeutic virtues for atopic dermatitis in infants.

To complete the discussion, still another remedy deserves mention—Vioform (Ciba), which chemically is 5 chloro—7 iodo—8 hydroxyquinoline. It has not enjoyed the popularity it merits although it is official in the National Formulary, ed. 8. Its results in the treatment of infantile eczema, as well as in the eczemas of older children, have been found good by others as well; in fact, on occasions it has proved to be the topical answer to eczema when orthodox treatment with the tars has failed. It may be used in strength of 1 to 3 per cent in ointment form, either with zinc paste, zinc ointment, or with ordinary petrolatum. It is also on the market as a 3 per cent cream—i.e., in a washable base, which makes it a satisfactory remedy.

13.—R Vioform	1.8
Petrolatum	60.0
Misce et fiat unguentum.	
Sig. Apply.	

Antipruritics may be added to any of the prescriptions given.

Röntgen therapy is certainly worth a trial after all other measures commonly adopted in the management of eczema have failed to bring about improvement. The dosage under such circumstances should be small—i.e., 36 röntgen units of low voltage radiation. It should be emphasized that treatment by means of röntgen rays should be carried out only by a skilled dermatologist who has been trained in their use and not by the pediatrician.

The use of the newer antihistaminic agents for the pruritus deserves brief comment. Benadryl and Pyribenzamine have at times helped to overcome the itching of which patients complain, but they have not proved useful to the same extent as in urticaria.

CONCLUSION

An attempt has been made to outline a simple and practical plan for managing atopic dermatitis in infants and children. Because all rational therapy must be based upon a clear understanding of the underlying pathologic changes, reference has been made to the fundamental principles of the dermatosis, both in its etiology and its mechanism of development. It appears that there is seldom need for the use of proprietary remedial agents in the management of atopic dermatitis because, happily, the dermatosis in all its stages can be treated adequately by chemicals and remedies contained either in the *United States Pharmacopeia* or the *National Formulary*. Further it appears that a few proved remedies judiciously employed are capable of doing more good than a large number of preparations employed without clear-cut indications for their use.

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Clinical Conference

CONFERENCE AT THE CHILDREN'S HOSPITAL OF MICHIGAN

PAUL V. WOOLLEY, JR., PEDIATRICIAN-IN-CHIEF

Case 1. Eczema Vaccinatum

DR. E. BRYCE ALPERN (Resident in Pediatrics).—This 14-month-old white child was admitted three days ago because of a rash of five days' duration. He has in the past had both asthma and eczema, but the latter has been manifest lately only by thickening and induration over the face and flexor surfaces of the extremities. Ten days ago he became irritable, lost his appetite, and passed several watery stools. Two days later a crop of "blisters" appeared on the areas involved earlier by eczema, and he was feverish and vomited several times. There were no eruptions in the remainder of the family, but a brother, with whom he was in intimate contact, had been vaccinated some thirteen days before appearance of the vesicles.

The patient was quite ill on arrival here, unhappy, and with a temperature of 102° F. The areas usually accentuated in infantile eczema—the face, elbows, and knees—were confluent masses of pustules resembling individually primary takes of eight or nine days' duration. Umbilication was present on most, but a few remained smooth while none resembled the earlier stages of vaccinia. Adenopathy was generalized and most marked in the axillae, where the nodes formed large tender masses. The trunk and other areas not predisposed by eczema were free from involvement. Laboratory data, obtained on the day of admission include a normal urinalysis, 5.9 Gm. per cent of hemoglobin, and 51,000 white blood cells per cubic millimeter, of which 49 per cent were eosinophiles and 32 per cent neutrophils showing marked toxic changes. The cerebrospinal fluid was normal in all respects.

On the day following admission the patient was worse and remained extremely irritable despite sedation and a return of the temperature to normal. Treatment had included a transfusion, 10 ml. of gamma globulin intramuscularly, full doses of penicillin and sulfadiazine, and a cellophane-heat cradle technique for protection of the skin. Yesterday he continued to deteriorate, and his temperature fluctuated widely. Several loose stools were passed, and during the afternoon he became quite dyspneic. This last development posed the question of acidosis, central stimulation, or decreased alveolar aeration. A plasma bicarbonate was 13 meq. per liter and the blood pH, 7.32, while a chest film showed no parenchymal pathologic change, and the cerebrospinal fluid was again not abnormal. The child was therefore handled conservatively, given sodium lactate and adequate fluids parenterally, and placed in an oxygen tent.

Today he is still comatose, his temperature remains unstable, and the eruption differs from that described on admission only by being three days closer to maturation (Figs. 1 and 2).

DR. PAUL V. WOOLLEY, JR.—This story illustrates the often repeated and often broken dictum: Do not vaccinate the contacts of eczematous babies. Our knowledge of several epidemiologic phases of eczema vaccinatum is incomplete, but in this instance, at least, we can reconstruct the story. (1) The sibling was vaccinated, responded with a primary take, and on the fifth day became involved with the systemic exanthematous disease, vaccinia; remember that this disease does not remain localized to a little spot on the arm but invades the host like other virus diseases. (2) Elementary bodies from this child were then passed to our patient and came to lodge on the skin areas previously prepared by eczema.



Fig. 1.—Eczema vaccinatum.

How this transmission was effected mechanically is open to interpretation, but the infecting particles are known to be present in both the developing pock and in the respiratory droplets. (3) As a result of these local implants our patient developed, some three days later, systemic evidences of vaccinia and, two days following, the cutaneous evidences of a primary take.

The treatment employed can be divided into three phases. First, he was given blood, plasma, and gamma globulin in the rather forlorn hope of modifying favorably the symptoms of vaccinia, per se. Several years ago we received a patient who had the misfortune to inoculate his conjunctiva at the time of vaccination so that the papular stage was reached in the eye and on the arm at the same time. Blood was obtained from a recently vaccinated individual, and

with this the patient was transfused. The papules at both sites underwent development resembling the classical "accelerated take" and did not scar. This led to such brief animal experimentation as the situation allowed, and we were able to show that in rabbits the use of human immune serum would prevent a take when injected during the incubation period and would prevent metamorphosis when used in the papular stage. We had no success in modifying the course of the primary take thereafter and hence, in the present patient, held little hope of benefit. Second, attempts to prevent secondary involvement of the damaged



Fig. 2.—Eczema vaccinatum.

skin by pyogenic organisms should be instituted, in this case by the use of penicillin and sulfadiazine. Finally, such supportive measures as will insure adequate fluid and electrolyte intake, optimal pulmonary ventilation, and stabilization of temperature should be considered. In the present patient we are still somewhat at a loss to explain the hyperpnea, and it is most likely a combination of central changes and mild acidosis. So far as the prognosis is concerned, I have little hope for this infant. In the excellent review by McKhann and Ross¹ a mortality of 30 per cent was anticipated, and the wide involvement, extreme toxicity, and failure so far to respond to therapy are not encouraging.

QUESTION.—What is the relation of eczema vaccinatum to Kaposi's varicelliform eruption?

DR. WOOLLEY.—I suppose that a liberal interpretation of Kaposi's description would justify placing cases of eczema vaccinatum in his syndrome, but he was more likely referring to the disseminated lesions of herpes simplex, from what we know today. He would certainly have recognized the similarity of this disease to the natural evolution of cowpox.

DR. JAMES L. WILSON (Professor of Pediatrics, the University of Michigan).—I think Kaposi's description covers best the clear vesicular eruptions seen in babies with any excoriated skin lesion. We see it as well in those with diaper rashes as eczema, and it is usually due to herpes virus or similar strains.

QUESTION.—Would the use of intracutaneous vaccination tend to avoid this complication?

DR. WOOLLEY.—Calf vaccine cannot be rendered sterile and should never be given intracutaneously. Vaccine propagated in tissue culture and eggs has been used but has not received wide acceptance. In any case it is difficult to see how its use would prevent spread since it is most probable that the vaccine particles are disseminated by the respiratory secretions.

QUESTION.—How can the diagnosis of eczema vaccinatum be established in the absence of a history of contact?

DR. WOOLLEY.—Vaccinia can be differentiated from all viruses other than variola quite simply by two means. When lymph from an active lesion is inoculated into the cornea of a rabbit, a typical lesion develops and the specific inclusions can be identified on section. A precipitin test, utilizing the lymph and a prepared antiserum, has been described by Paul and is quite specific.

Final Note

This patient died on the day following presentation and was discussed at the weekly Clinical Pathological Conference of Dr. W. W. Zuelzer. A surprise finding was an extensive pulmonary process, which had not been detected clinically and which undoubtedly explained to a considerable extent the hyperpnea noted during life. The exact nature of this was not clear although the distribution fitted an aspiration pneumonia better than an infectious process. Two patients with eczema vaccinatum seen since this one have survived, but neither had the widespread confluent lesions described in this child.

Case 2. Rickets Resistant to the Usual Doses of Vitamin D

DR. WOOLLEY.—Since this patient has not been in the hospital recently, it will save time if I review the history. He is now 25 months old and was seen here first some five months ago because of rickets. During the first eleven months of life he had developed normally, and nothing out of the ordinary had been noted either by the parents or his physician. He then stopped standing or attempting to walk, although both levels had been attained earlier. For the next

four months he appeared increasingly unhappy and seemed, at times, to have pain in his legs, and he ceased even to creep. In March, 1947, when he was 15 months of age, x-ray films of the extremities were said to show rickets although daily doses of percomorph oil in roughly 1,500 unit amounts had been given since the child was 3 weeks of age. During the summer of 1947 he was given 9,000 units of vitamin D daily, one third as percomorph oil and the remainder as viosterol, as well as thorough exposure to sunlight, but no clinical or roentgenologic evidence of healing appeared. Dr. Glen Hanse, one of our staff physicians, saw him in September, 1947, and brought him here for study; we have followed him together since that time.

A review of his family and past histories has not been helpful except that the mother has kept admirable records which support her contention of normal growth and development prior to 11 months. Physically, at 20 months, he was rather small, measuring 29.5 inches and weighing 30 pounds. He was well nourished for his size but the musculature felt soft and relaxed, while bowing of both the arms and legs was grossly obvious. His head was well formed and free from stigmas, but the ribs flared and beading of the costochondral junctions was pronounced. The abdomen was prominent and the wall thin. When supported he would stand and even take a step or two in a waddling and unenthusiastic manner. Films obtained at admission (Fig. 3) will be shown shortly by Dr. Evans; they confirmed the impression of active rickets.

Our immediate study of this child followed the lines stressed in these clinics on several occasions. Renal disease was discounted by several normal urinalyses including specific gravities of over 1.025, by blood urea determinations consistently within the usual ranges, and by good concentration of Diodrast. There was nothing to suggest liver dysfunction, if such per se is ever the cause of rickets, since both the prothrombin level and the cephalin flocculation tests were satisfactory. Blood calcium levels consistently below 8 mg. per cent accompanied by blood phosphorus determinations ranging from 1 to 3 mg. per cent are not typical of any parathyroid disorder, while absence of cystine crystals, urine free from sugar or albumin, and a normal bicarbonate content of the blood did not suggest the Fanconi syndrome or a "metabolic defect." This then left us with two plausible possibilities, a failure to absorb vitamin D from the intestine, or a failure to respond to the usual levels of absorbed vitamin. The first was discounted temporarily by inference since there was no difficulty in absorbing fat and since vitamin A was adequately handled; later this was ruled out definitely by giving vitamin D intramuscularly without healing. We therefore began to give increasingly large doses of vitamin D orally and to follow the child's progress periodically with blood calcium, phosphorus, and phosphatase determinations as well as with monthly roentgenograms.

During October he received a total daily intake of 75,000 units, of which one-third was percomorph oil and the remainder viosterol. Five grams of calcium lactate were given concomitantly. At the end of the month there were no changes in the films, the blood calcium and phosphorus were still reduced, and the phosphatase remained at 30 Bodansky units, where it had been during hospitalization. Early in November an additional 25,000 units as percomorph

oil were given, but this, as might be expected, resulted in gastrointestinal symptoms so that he received during the remainder of the month 100,000 units as viosterol and 25,000 units as pereomorph oil. During this period the parents were instructed to offer orange juice liberally, and the child's daily consumption was usually around 16 ounces. Some response was obtained on this regime since by December the blood calcium was 10 mg. per cent and the phosphorus 3.8 mg. per cent. No positive evidence of healing was reported roentgenoscopically, and the phosphatase was 67 Bodansky units. During December he was given, in addition to orange juice and calcium salts, 150,000 units of viosterol and 25,000 units of pereomorph oil, and today (Jan. 12, 1948) his calcium is recorded as 9 mg. per cent with the phosphorus up to 4.6 mg. per cent. The phosphatase has fallen to 32 Bodansky units, and Dr. Evans is able to demonstrate unequivocal evidence of healing.

DR. W. A. EVANS (Roentgenologist-in-Chief).—This film (Fig. 3), taken last September, shows marked flaring and irregularities at the ends of the diaphyses, and there has been no deposition of calcium in the metaphyseal new bone for some time. The periosteal new bone is also low in calcium content. These findings are characteristic of severe rickets of long standing, of at least ten months by our measurements. There is considerable bowing of all the long bones.

These films taken during October, November, and December show no essential deviation from those described earlier, although, in retrospect, there possibly was a little increase in density of the osteoid in the December set. Here are the films for yesterday (Fig. 4). There has been considerable ossification at the ends of all diaphyses as well as extensive alteration in the appearance of the periosteal osteoid. The metaphyseal areas remain irregular, which means that we still have not effected complete healing.

QUESTION.—What interpretation can be given the phosphatase values in this case?

DR. WOOLLEY.—These were continually elevated, with the highest value of 67 being recorded in December and falling to 32 yesterday. It is difficult at times to explain phosphatase changes, but I think if we forget specific cases and look upon it from Albright's generalization that phosphatase goes up when there is increased osteoblastic activity, such as in response to stresses on osteomalacic bone, certain discrepancies disappear. When this boy was confined to bed and had neither the desire nor the ability for weight-bearing, the phosphatase remained only moderately elevated—in the thirties. In December, when his parents reported increasing activity and marked improvement in disposition, it went up to double the former level even though the blood chemistry would suggest a state optimal for healing. Now the phosphatase has come down as healing takes place; isn't that likely to reflect decreased osteoblastic activity as the bones become mechanically better able to cope with weight-bearing?

QUESTION.—Isn't there considerable danger in using such large doses of vitamin D over a protracted time?

DR. WOOLLEY.—It has been pointed out that the greatest danger of overdose with D lies in raising the calcium level to a point where kidney damage ensues. With this patient we have not worried too much since repeated blood determinations have consistently shown a hypocalcemia. We have taken the additional

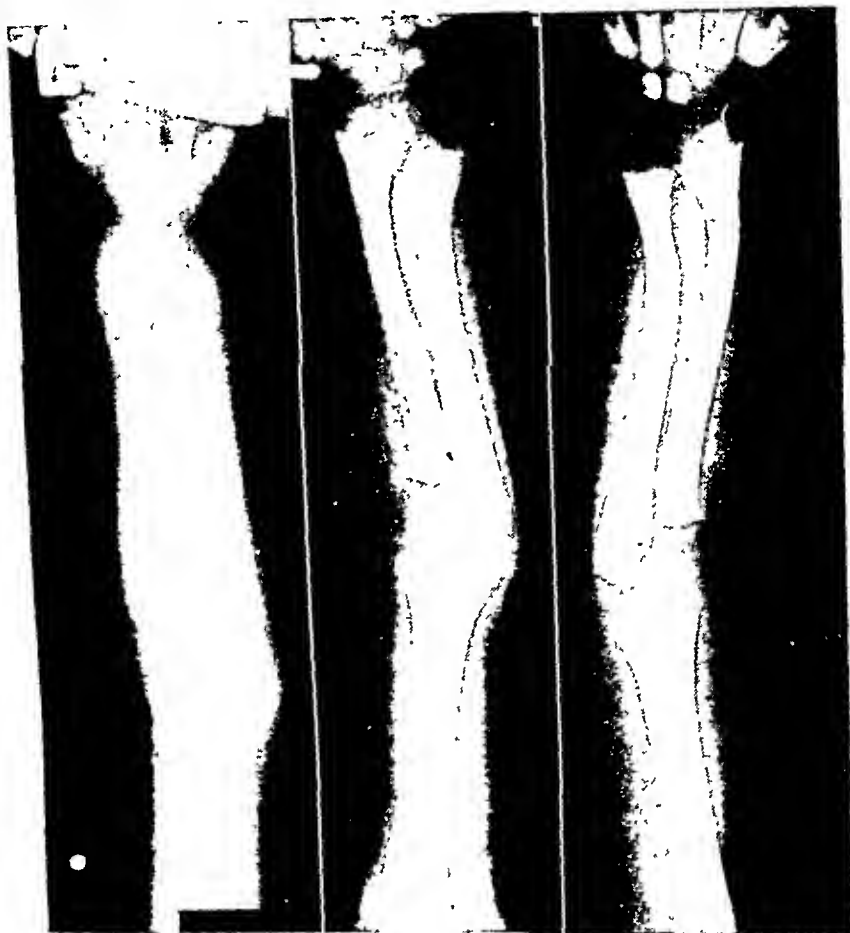


Fig. 3.

Fig. 4.

Fig. 5.

Fig. 3.—Resistant rickets, September, 1947.

Fig. 4.—Resistant rickets, January, 1948. Note extensive calcification with continued irregularity at the epiphysis.

Fig. 5.—Resistant rickets, March, 1948. Healing now complete.

precaution of having his mother check two specimens daily with Sulkowitch's reagent, and to date she has not detected calcium excretion. I think that now healing is proceeding we will have to be doubly cautious, and she has been warned to notify us immediately upon obtaining a positive reaction. We will then have to adjust the child to a maintenance vitamin D intake which will assure continued calcification without excessive calcium loss.

Dr. Johnston, do you have any pet theories on such patients? It is to me a fascinating fact that we have a biologic reaction which requires 250 times the

usual amount of a reagent in order to effect a comparable result—even though absorption does not seem to enter the problem. It seems almost as if some individuals did not utilize the usual form of D but required an isomer occurring as a contaminant in a ratio of maybe 1:250 in standard oils.

DR. J. A. JOHNSTON (Pediatrician-in-Chief, the Henry Ford Hospital).—I have no explanation for refractive rickets and know of no one else with any satisfactory theory. We have found that the addition of a small amount of thyroid seems to speed up healing in patients with rickets, but this is probably a nonspecific reaction since there certainly is little common to both hypothyroidism and rickets.

Final Note, April, 1948

Healing by x-ray is now complete (Fig. 5). On March 11, 1948, the mother reported a strongly positive Sulkowitch test and all medication was stopped. The test became negative in three days, and the child is now on 75,000 units daily and shows only occasionally a faint clouding with the reagent.

Case 3. Amebic Dysentery

DR. ALPERN.—This little Negro girl is now 19 months old and has been admitted because of bloody stools passed over the last four weeks. She was here for a few days earlier in the month with the same complaint but complicated by a severe upper respiratory infection, which was thought to account for her symptoms so that not enough attention was paid to other possibilities, although she was proctoscoped and nothing was found.

Her stools during the period of illness have numbered from three to twelve daily and have been of the usual color, but are frequently streaked with mucus and usually followed by the passage of about a teaspoonful of recognizable blood. They have not been tarry, and she has had no abdominal pain or loss of appetite.

Physical examination showed little to lead to a diagnosis, and the urine, blood cell counts, tuberculin test, and Mazzini test were all within the limits of normal. A stool was semiformed and streaked with blood and mucus but no pus. Cells resembling amebas were seen, and these contained red cells and agreed in size with the usual limits for *Endamoeba histolytica*. Only two cysts were found in preparations stained with iron hematoxylin, but they were quite typical of the pathogenic species. The patient was again proctoscoped, this time with a longer instrument, and near the rectosigmoid junction were found numerous discrete and punched-out ulcers, many of which were covered by gray membranes. The remainder of the mucosa was normal. Smears taken directly from the ulcers were loaded with trophozoites.

It is interesting that this child's father was in the Army and, while he was not in the war zones, did have several bouts of diarrhea. He is being treated by the Veterans' Hospital for abdominal symptoms attributed to duodenal ulcer. His physician has been contacted and will examine the remainder of the family.

DR. WOOLLEY.—This case needs little comment except to say that we all missed the diagnosis during the first admission and that infants do contract

amebic dysentery even though it more typically strikes an older age group. I have recently talked to two internists, both former service men and both on the Veterans' faculty, who tell me that there is plenty of amebic dysentery in the Detroit area, once it is looked for and once proctoscopy becomes a routine part of the gastrointestinal study. The laboratory diagnosis, as most of us who saw it in service know, is not difficult. The trophozoites occur during active ulceration and can be found in freshly passed stools or in swabbings from the lesion. The cysts are characteristic of periods when diarrhea has abated and are best studied after staining. Positive differentiation of pathogenic from the saprophytic amebas still remains a problem for the laboratory specialists. Dr. Alpern, how do you propose to treat this child?

DR. ALPERN.—It is generally recommended that Diodoquin or carbarsene be used in children rather than emetine or Yatren. We have already begun Diodoquin in daily dose of $\frac{3}{4}$ gr. per pound and will keep this up for three weeks and follow it with two weeks of carbarsene.

Final Note

No blood was found in this child's stools after two days' therapy, and the ulcers were found by proctoscopy to be healed at the end of one week. No complaints were elicited at her monthly return visit.

Case 4. Pyloric Stenosis

DR. MARY JANE STERN (Resident in Pediatrics).—This 5-week-old boy was admitted yesterday because of vomiting since birth. The mother stated that emesis occurs a few minutes after almost every feeding and has gradually become more and more forceful. Stools during this period have been scanty, and a cathartic has been given daily. Treatment at home has been limited to frequent changes in the amount and constitution of the formula, but despite such measures the weight has fallen from 7 pounds, 1 ounce at birth to 5 pounds, 12 ounces on admission here.

Examination showed the child to be serawny, hungry, and dehydrated. The respirations were shallow and very irregular. A typical pyloric tumor was easily felt, and the vomiting on trial feeding was forceful and immediate. Laboratory information included a normal urine with a pH of 9, 15.9 Gm. of hemoglobin, a normal white blood cell count, and a negative Mazzini test. The serum bicarbonate was 41.8 meq. per liter and the blood urea nitrogen 48.7 mg. per cent.

It was obvious that the patient, besides being dehydrated and in a poor nutritional state, was in severe alkalosis. He was given a mixture of oxygen and carbon dioxide by inhalation and then 90 ml. of $\frac{1}{6}$ N ammonium chloride subcutaneously as well as plasma and glucose intravenously. The blood bicarbonate fell to 23.7 meq. per liter in six hours, the baby clinically was markedly improved, and the usual Fredet-Rammstedt procedure was carried out this morning without incident.

DR. WOOLLEY.—This patient is shown for three reasons. First, since we have become so highly sensitized to the possibility of pyloric stenosis it has be-

come a rarity to see a baby in the state of this one. Some eighty patients have been admitted for surgery in the past two years, and I believe this is the first in whom severe alkalosis was a problem; usually nothing other than mild pre-operative preparation is in order. Second, we call attention to two means of controlling alkalosis—carbon-dioxide inhalations, and the more rapid and more exact technique of parenteral ammonium chloride, a method popularized largely by the St. Louis group.² Finally, this gives Dr. Evans the opportunity to discuss the roentgenologic diagnosis of pyloric obstructions.

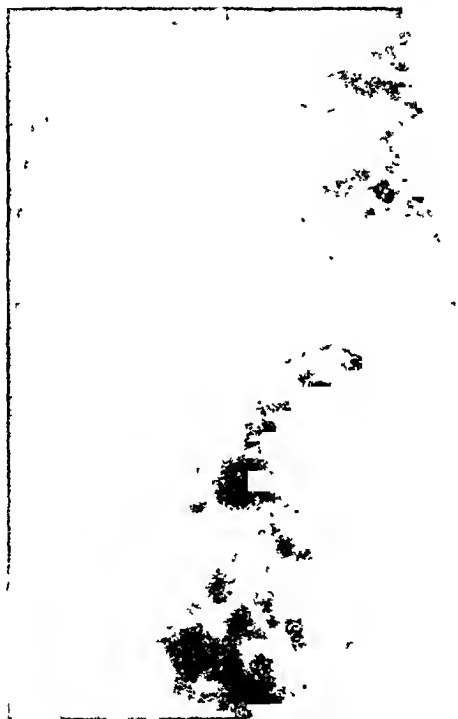


Fig. 6—Normal stomach, pylorus, and duodenum.

DR. EVANS.—In the past we have not often been called upon to demonstrate hypertrophic pyloric stenosis roentgenographically, since the story and physical findings have been considered sufficient for diagnosis. There are, however, occasions when confirmatory evidence is desirable, especially when a tumor is not palpable and a functional obstruction is under consideration or when an organic anomaly other than hypertrophic pyloric stenosis is suspected.

It is necessary, for the satisfactory study of the stomach, duodenum, and pylorus in infancy, to have the mucosal surfaces washed free of mucus and the stomach emptied of air, food, and secretions. Feedings should be withheld for twelve hours and, if the stomach appears distended, a tube should be in place during this period. Lavage is then carried out until the returns are clear. A thick suspension of bismuth, which will cling to the surfaces, is desirable; only about 5 to 10 ml. of this should be given. This film (Fig. 6), recently obtained

on a patient suspected wrongly to have a pyloric obstruction, shows the normal appearance of the stomach, pylorus, and duodenum. Note that the column of barium passes freely from the stomach in a sizable stream and that the pyloric impingement is of only short duration. These films (Fig. 7), in contrast, are from a patient with proved hypertrophic pyloric stenosis. The upper two films illustrate the difficulty of examination when the stomach is distended by gas and

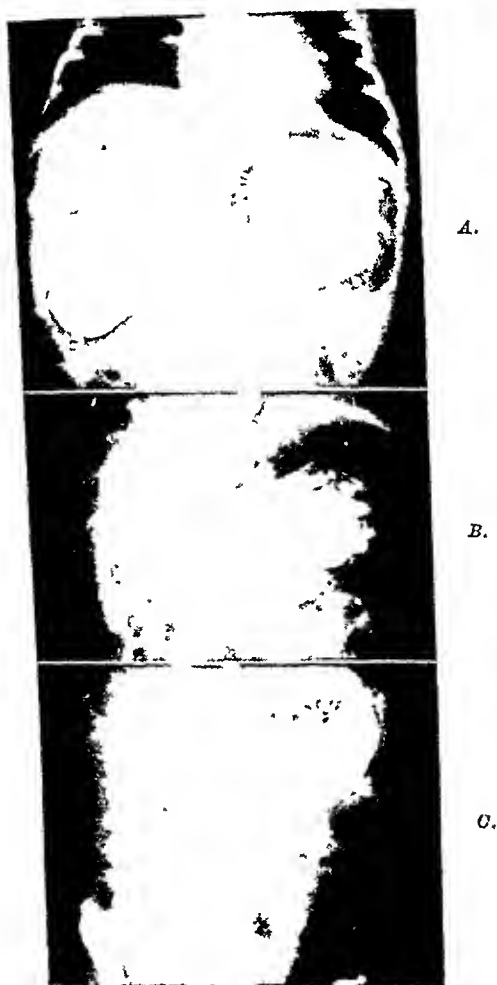


Fig. 7.—Hypertrophic pyloric stenosis. A and B, films without correct preparation showing merely dilatation and gaseous distention. C, following correct preparation and now showing classical signs of pyloric stenosis.

liquid. The lower film study was made after preparation by aspiration and lavage of the stomach, and the long narrow pyloric canal is well demonstrated (the string sign). We can also see that the barium located at the pyloric end of the stomach assumes a concave aspect, this is due to impingement on the usual contour by the hypertrophied pylorus. For completion we show this film (Fig. 8), illustrating a partial obstruction within the duodenum itself. Note that the

pylorus as well as the first portion of the duodenum is normal, in contrast to the constriction seen with hypertrophic pyloric stenosis. There is gaseous distention of the descending loop of duodenum with small amounts of gas in the small bowel beyond, indicating a partial obstruction in the distal duodenal segment. At operation, peritoneal bands were found obstructing the duodenum proximal to the ligament of Treitz.



Fig 8 —Duodenal obstruction (partial) due to peritoneal band. Note dilatation of first portion of duodenum.

QUESTION.—How much attention can you pay to the size of the stomach and to the emptying time? .

DR. EVANS.—Neither is reliable. The stomach is easily distended by air, and hence size is entirely relative. So far as emptying time goes, this also is extremely variable, depending upon gastric motility and activity as well as relaxation of the normal pylorus and absence of obstruction.

DR. JOSEPH A. JOHNSTON (Henry Ford Hospital).—Even when a tumor is palpable it is important to appraise the clinical history and to resort to x-ray if a reasonable doubt exists. We have recently seen a child operated upon after all of us had felt what we took to be a tumor but which turned out to be a dilated and hypertrophied duodenum due to obstruction lower down.

DR. ALLAN RICHARDSON (Senior Pediatrician).—The ability to feel a pyloric tumor varies greatly with the individual. Dr. David Levy, the dean of pediatricians in this area, claimed that he had never palpated one with certainty. It requires for all of us a certain amount of persistence and patience but has, in my experience, been rewarded by absolute diagnosis.

DR. OTTO GROB (Senior Pediatrician).—A very important point brought out by this patient is that it is all right to handle vomiting babies with conservative medical treatment, such as phenobarbital, atropine, and thickened feedings, so long as the child is not losing ground. However, as soon as weight loss appears, it is time to institute more drastic study and to consider a truly obstructive lesion.

QUESTION.—Is there any satisfactory answer to why patients with pyloric stenosis begin to show symptoms only after several weeks of normal life?

DR. WOOLLEY.—This is a question that has received attention for years, and there is today still no concrete information on the pathogenesis of the disease and no explanation for the male predilection. We were taught, some ten years ago, that the tumor was congenital and that vomiting of a projectile type developed only after the stomach could hypertrophy. Others have long contended that the hypertrophy is present at birth but that a second element, spasm, must be added later to cause typical clinical symptoms. Still others believe that the time of onset of both hypertrophy and spasm varies and may be present before birth or develop during the first few weeks of life. We have all been interested in Dr. Wallgren's recent experiment,³ in which he performed gastrointestinal series on 1,000 consecutive newborn boys, of whom five later developed clinical and roentgenologic evidence of pyloric stenosis. When he reviewed the original films taken on the five he could find nothing to distinguish them from the remainder of the newborn group.

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Psychologic Aspects of Pediatrics

PSYCHOLOGY IN PEDIATRICS

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PSYCHOLOGY as an inextricable part of medical functioning has yet to become a formal constituent of the medical curriculum. The dynamic psychology of the twentieth century introduced the neurosis as an embracing term which exonerated the physician of responsibility in those distressed cases yielding no demonstrable organic components; the organically oriented practitioner either impatiently nursed his "neurotics" along or shifted the burden to the psychiatrist. This dichotomy in treatment cannot operate in the best interest of the patient or of medical progress.

There is some doubt that the neurotic's sufferings are altogether functional; it seems likely that improved diagnostic techniques will reveal some covert organic defect in that physiologic system through which the conflict is expressed. Psychologic tests of neurotics disclose consistent impairments in mental efficiency, possibly dependent on neurological correlates. Gesell⁹ expresses this succinctly: "Thought structures are just as real, just as somatic, as crystal and fiber structures. . . . The induction forces which operate at the lofty psychical level of creative thinking are subtle and complex, but they cannot be different in essence from those which shape the soma. Thought structures are in fact the ultra-electronic histology of the soma. . . . The long deferred clinical symptoms trace back to early life. As in neurology, so in psychiatry there are many genetic phenomena which can be understood only in terms of developmental mechanisms."

Whatever may prove to be the relative contribution of the organic and the psychologic in the neurotic illness, there is no doubt of the inseparable cyclical interaction in that group of diseases now labelled psychosomatic, whose manifestations are unquestionably those of somatic disease processes. That these and even infectious diseases are predisposed and exacerbated by psychic factors has been demonstrated many times. Day³ found consistent psychic trauma previous to the development of tuberculosis in young persons. Bronchial asthma reveals a large psychogenic component.¹⁰ According to Richardson,¹⁶ infectious disease develops only when the individual has reached the breaking point; it is no longer easy to conceive of asthma or ulcer or obesity as a characteristic only of the individual; they must be considered as part of the family and the larger environment.

That psychologic tension plays an important role in lowering the threshold of resistance is an important clue to the possible threat of more calculable

This paper is an abridgement of a chapter which will appear in *Applied Psychology*, edited by Fryer and Henry, to be published in the near future by Rinehart and Co., New York.

environmental interrelationships. The ready response of the autonomic nervous system to mental stress in producing genitourinary and gastrointestinal difficulties, the dependence of vascular disaffections on environmental disturbances, and the fluctuation of mental level due to asthenia, endocrine imbalance, or disease process, all allow the broad generalization that "every organic disease, temporary or permanent, contains a functional factor; and every functional disorder is accompanied by some physical change of secretion, excretion or motor function which in time affects tissues."²⁰

How, then, can medical practice be conducted without psychologic training? The patient at present falls between the Scylla of the organically oriented physician who usually ignores the psychologic implications, and the Charybdis of the psychiatrically oriented practitioner who often ignores the organic implications.²¹

Whatever the psychologic delinquencies in adult medical therapy, they cannot be tolerated in pediatrics. The pediatrician has access to continuous anamnesis; he is aware of the mother-child relationship; he can observe and help to shape the physical and emotional adjustment of his patient. He has the grave responsibility of anticipating the interaction of environmental pressures and constitutional weaknesses and predispositions. Without adequate guidance, a faulty interaction establishes the foundation of adolescent and adult personality and somatic problems.

Only the youngest pediatricians have received even minimum psychologic training. Short of achieving the ideal state in which the pediatrician is as learned psychologically as he is medically, the simple solution would seem to be a closer conjunction between psychologist and physician. The physician now refers only the most glaring behavior disorders to the psychologist. Not only has the rewarding period of possible prophylaxis been missed, but the situation has already been aggravated by concomitant family tension arising from the child's maladjustment.

Behavior disorders are, however, an already extreme symptom of poor integration. Less discernible are psychogenic factors in apparently organic disturbances, such as asthma, colds, diabetes, and dermatologic conditions. Eleven asthmatic children¹⁵ presented basic conflicts revolving around an exaggerated fear of separation from the mother; there was strong evidence that the specific emotional condition was at least of equal importance to the allergic sensitivity in the production of asthmatic attacks.

In a five-year study of nursery school children,⁴ the highest incidence of colds appeared in children from broken homes; anxiety and frustration stemming from traumatic situations induced internal tensions whose operation may be assumed an important factor in contributing to susceptibility. Other workers,¹⁴ applying criteria of normality to diabetic children, discovered an earlier onset of the ailment among the markedly deviate than among the normal. Twice as many of the abnormals had frequent ketosis. Purely medical treatment of the diabetic child must therefore remain inadequate.

Dermatologic and allergic phenomena may be deeply rooted in childhood reactions to a congenital weakness. Deutsch and Nadell⁷ trace several presuppositions for the development of chronic allergies and related skin conditions:

skin symptoms in early childhood probably originating on a genetic basis; a deviation or fixation of instinctual drives during the earliest psychic development and fusion of these with the different sense perceptions related to the skin; complementary neurotic traits of the environment favoring the amalgamation of the psychosomatic entity; development of a narcissistic and exhibitionistic personality pattern tinged with compulsive neurotic traits.

The permeation of psychologic factors in the child's development in illness and in health makes psychologic services as vital an adjunct to pediatrics as the tests of the medical laboratory. "The psychology of the child, which includes all his behavior, is inseparably bound up with his nervous system and indeed with his entire organism."¹¹

Because of its relative novelty and because competent psychologists are few, psychologic service is, on the whole, limited to children with school maladjustments, with serious behavior disorders, and to those in penal or mental institutions. Yet the so-called normal child might yield the best guidance dividends by achieving an adjustment unsusceptible to illness, flexible to unavoidable illness without traumatic sequelae, and otherwise comfortably integrated and mature. Suranyi¹² saw noticeable differences in normal children at birth, and observed that some were from the beginning adored by everyone, some with special talents endeared themselves to a few, and some aroused antipathy in nearly all who came in contact with them. He concluded that attempts to account for these reactions on the objective basis of physical appearance or classifiable behavior were futile. There seemed to be not single gross traits but an exceedingly large number of minute factors, each too small to be regarded as significant in itself but constituting a large responsible aggregate. Many children now considered normal are in need of help; there is need of a more adequate criterion for selecting them and for the recognition of small signs of instability. Accordingly, psychologic guidance might well be a part of the routine medical checkup of even the normal, healthy child.

THE MENTALLY HANDICAPPED

The small signs in the normal child loom large in the infant handicapped by genetic factors, uterine accidents, birth injuries, anoxia, disease sequelae or endocrine imbalance. From the beginning such a handicapped child requires medical care and supportive psychologic therapy. Without the aid of psychologic tests, it is often difficult to determine the cause and degree of mental retardation or deficiency, of personality deviation, or of speech and sensory impairment.

There is, for example, a distinct difference in the thinking processes of the mentally deficient child and of the child who shows evidence of an early acquired brain lesion. The latter stresses the functional properties of objects and the concrete elements of the situation. He elaborates on detail, changes meanings of objects to suit present associations, and is unable to move beyond the given situation in space and time; his intellectual processes appear impaired, his performance is erratic and uncontrolled. The mental defective, on the other hand, shows a test pattern more controlled and less erratic, but with a limitation in most intellectual areas.

Mental deficiency and retardation derive from a varied etiology. There may be present the simple genetic factor of inferior intelligence or the results of an Rh blood incompatibility of mother and child. The exsanguination-transfusion treatment of the hemolytic diseases as a means of avoiding mental deficiency has yet to be validated.

The encephalitides following infectious diseases, congenital paresis, lead poisoning, endocrine imbalance, defects in fetal development, birth injuries, premature birth, and malnutrition, all take a toll either in frank mental impairment and retardation, in impairment of mental efficiency, or in personality disturbances.

For many of these conditions, where actual mental impairment or retardation exists, there is little medical help. But psychologic guidance can shape the environment to provide maximum satisfactions with the patient's limited resources, to remove stresses and strains, and to lighten the complicating burden of parental guilt and unhappiness.

The effects of thyroid deficiency, if recognized and treated very early, can be somewhat mitigated. Though there is a relationship between early adequate therapy and subsequent physical development, caution is indicated in predicting mental growth. The rate of spontaneous functional progress before the initiation of treatment is a more reliable basis for intellectual prediction than either the time of beginning treatment or the dosage.²

The premature child will probably show mental or emotional retardation for some time, the degree of retardation depending on the degree of prematurity. Nor can it be determined at what point in the developmental cycle mental growth corresponds with chronological age. Studies of visual acuity⁸ suggest some lag in the sensory development of the premature infant. Quite opposed to the theory of retardation in the growth cycle of fetal infants is Gesell's⁹ unqualified observation: "Uncomplicated prematurity imposes no handicap on development. The majority of premature infants are normally endowed and, given proper care early in life, their development is entirely normal. They cannot, as children and adults, be distinguished from individuals born after a full-term gestation."

BEHAVIOR DISORDERS

Malnutrition may exist in actuality or only in the mother's imagination. Ingestion, digestion, and elimination are the child's earliest affective associations. They may aid in establishing a warm mother-relationship, or they can become powerful weapons for punishment and revenge. Grim emphasis on feeding and toilet schedules, scolding and coaxing, lengthy and fussy eating sessions, insistence on quantitative intake or on special foods, all add up to early eating and bowel difficulties and subsequent physical and emotional complications. Many of these problems, for which she pays a high price, are rooted in the mother's own hostility and neurotic maladjustments. When pediatrician and parent recognize that each child is a variable dynamo with a uniquely constituted nervous system and an individual developmental tempo, a large number of these behavior disorders disappear.

Protests against emotional deprivation and environmental frustration take the form of emesis, breath-holding, tantrums, excessive crying, provocation of convulsions, head banging, and the like. Having achieved satisfactions subsequent to an involuntary occurrence, the child is thereafter voluntarily induced to reproduce the initial success. Effective measures are, first, a relaxed indifference to these episodes when they occur, and second, therapeutic psychological attention to the conditions that produced them; or better still, a reversal of this order when the problem can be intelligently anticipated.

A wide assortment of other tension-releasing devices appear: Restlessness, anxiety, unnatural fears, and feelings of inferiority express themselves in nail-biting, thumb-sucking, enuresis, masturbation, hair-plucking, ties, stuttering, and other behavior patterns. All require professional attention, not only to give the child relief, but because they may be symptomatic of graver maladjustments still to come. The mother's distress and involvement in the problem automatically disqualify her for finding the solution alone.

Any of these behavior disorders may appear transiently in the normal child. But the neurotic, neuropathic, or psychopathic constitution presents them in constellation and more or less permanently. Uncertain as the somatic diagnosis now is, there is reliable evidence that physiologic correlates exist to undermine resistance to even the less harsh onslaughts of the environment. A simple illustration is the infant's undue distress after swallowing air. Most infants swallow air during feeding, but those suffering from it are the kinetic type who gulp food. Rumination is a neurosis, the elucidation of which may be puzzling.¹ The pleasure derived from it induces the repetition of a once-involuntary regurgitation; this is the familiar pattern of psychological dynamics imposed on a substratum of somatic defect.

Hysteria, a common psychoneurosis in childhood, is marked by exaggerated impressionability and suggestibility. Disturbed visceral function, motor disorders, and distorted emotional responses are the defense mechanisms adopted to safeguard ego and preserve self-respect.

These instabilities are in some measure physical as confirmed by a study by Sherman and Jost,¹⁷ which concluded that, in general, the neurotic appears to be much more unstable physiologically than the normal child. For the neurotic, neuropathic, and psychopathic individuals, medical and psychological supervision are mandatory through childhood and adolescence.

Enuresis, as an expression of anxiety, sexual excitement, resistance, defiance, and immaturity, is an extremely common behavior disorder. To the well-known dynamics, Despert⁵ adds the neurotic attitude of those responsible for training children in urinary control. In this group, she observed that though the enuretics ate and gained well as infants, psychomotor development was relatively late. They early experienced difficulty in expressing normal aggressive impulses and persisted in infantile demands far beyond the usual age levels. While not true in all enuretics, in some cases very early training results in overorganized personality patterns with compulsive tendencies. Enuresis rarely succumbs to physical measures alone.

The fearful child and the anxious child present different behavior syndromes. Fears develop from the trauma of actual experience and, unlike anxieties, exist on the conscious level. The child exposed, for example, to surgical operation manifests emotional sequelae definitely attributable to this experience. Prolonged night terrors are characteristic responses of the one- and two-year-olds; those above 4 often become negativistic. The presence of the mother and the administration of anesthesia before removal from the hospital bedroom will sustain the young child through a trying experience when it cannot be postponed.¹³ In the face of night terrors, simple hypnagogic suggestion is often effective.

DEAFNESS AND SPEECH DISORDERS

Deafness of any degree gravely influences personality adjustment. The totally deaf child does not progress beyond prelinguistic babbling in which utterance is unaffected by auditory impressions. Both hearing aids and rehabilitation at the earliest possible moment are recommended for total and partial deafness.

Stuttering and other forms of speech disorders have long presented a challenge. Actual structural defects remedial by surgery or palate plates are relatively rare. The victim of cleft palate is understandably resentful and humiliated, and, as a result of this, often aggressive. Speech difficulties and behavior patterns derive from clear-cut causes. Lispings, too, presents a simple diagnosis of poor dental spacing or the indulgence and perpetuation of infantile speech habits. Nasal speech may be due to polyps, adenoids, or tonsils, and slowly developing speech to poor auditory perception. Much more subtle, however, are the mutisms, disorders of articulation, and stuttering.

The speech-defective child displays a variety of personality difficulties, of which speech is only one expression. Overprotection may eliminate the need of speech, gesticulation providing a good substitute. Low or retarded intelligence influences the rate of speech development, or for protective reasons the child prefers to remain at the infantile level. Special education in a nursery school is imperative for these disabilities.

Stuttering is attributable to both physical and mental disturbance, and appears during the more stressful periods of growth: from 2 to 4 years of age when the mechanisms of speech are integrating; from 6 to 8 years when school pressures are new; and in early adolescence with its physical, emotional, and social hazards.

A recent symposium on stuttering⁶ revealed a many-faceted syndrome in the production of the stuttering personality. That anxiety is primary, not secondary, to the speech difficulty is an outstanding finding. The majority of the fifty children studied made a poor social adjustment very early, even before the speech defect could be considered a serious social handicap. In addition, handedness, contrary to a prevailing concept, played no part as a single etiological factor. The subjects' families had a higher than average ratio of upper respiratory, upper digestive, and cardiovascular diseases. From this the investigators conclude that the hereditary factor might be interpreted as a

somatic selectivity influencing symptomatic choice in the stuttering individual.

In the same study, stutterers revealed a marked disturbance of motor function. Even in those children who did not present motor retardation, analysis showed a global, uniform defect in maturity of the extrapyramidal system. Rorschach patterns of the same group disclosed emotional and personality maladjustments, rigidity, great anxiety, and obsessive-compulsive traits.

Johnson¹² focuses attention on a previously neglected factor—namely, that stuttering in serious forms seems to develop after diagnosis rather than before it, and is, therefore, a consequence of the diagnosis. This may imply that formal medical recognition of his difficulty poses a new problem for the stutterer.

Too often parents and teachers attach disproportionate importance to the stuttering while minimizing the personality and neurological correlates of which it is only an expression. Probably underlying both the stuttering and the parental reaction, however, is a poor parent-child relationship, lack of parental response, and a resulting feeling of insecurity.

NEED FOR PEDIATRIC-PSYCHOLOGIC COOPERATION

There seems to be little doubt that the pediatric approach must be in large measure psychologic. Pediatrician and psychologist must work together in close teamwork, not only when personality organization provokes the disease syndrome or is adversely affected by it, but when routinely guiding the apparently normal child.

Caution is in order lest a tendency to overstress the psychogenic aspects ignore the simple physiologic evidence. The myopic child expresses his discomfort in a variety of seemingly neurotic patterns. Night terrors and even asthma may result from difficult breathing arising from bad tonsils or adenoids. The apparently wilful and disobedient or suspicious child may be laboring under a hearing difficulty. Sexual derelictions may begin with itching, irritation, or inflammation of the genital area. Inattention, lassitude, and indifference can often be laid to malnourishment or fatigue. The psychologist shares with the pediatrician, therefore, the obligation to consider all the possible factors before exercising his special skills.

Because the dynamics of the young personality are not yet clouded over by the cornified layers of resistance to social pressures and conformity, simple psychologic measures usually suffice. In many cases, therapeutic hours spent with the parents are more rewarding than those spent with the child.

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Comments on Current Literature

ATOPIC ECZEMA AND BRONCHIAL ASTHMA

THE relationship between atopic eczema in infants and respiratory allergy, especially bronchial asthma in older children, is of practical importance in the over-all management of the allergic child.

In a recent article Ross and Brown¹ state that about one-third of infants with atopic eczema develop other allergic manifestations in later life. They urge that allergic children be given the advantage of protection from repeated exposure to animal danders, feathers, and house dust, since a significant number of such children will develop, within a period of months or years, positive skin tests to these inhalants associated with attacks of bronchial asthma. By employing such preventive measures, it seems reasonable that a certain number of children with allergic tendencies might be spared untoward clinical manifestations.

In an article entitled "Food Sensitivity in 100 Asthmatic Children," Lewis Webb Hill² points out, on the other hand, that the persistence of cutaneous sensitivity to food may lead to erroneous interpretation of such skin tests and may result in serious mistakes in therapy. Although positive skin tests often persist and the cutaneous reaction may be as large as it was in the beginning, there is a great tendency in allergic children to acquire tolerance to food as they grow older.

As an example of uncritical interpretation of skin testing, Hill refers to a 5-year-old child with bronchial asthma who had been placed on a ridiculous diet, based upon results of 236 tests for food. She had been found skin-sensitive to 109 foods. "The asthma was in reality due to grass and tree pollen, and she was later quite successfully hyposensitized, with no dietary restrictions whatever."² While Hill states that food can cause asthma in children, he emphasizes the fact that cutaneous sensitivity to food is often not correlated with clinical manifestations of allergy. He studied 100 asthmatic children between the ages of 3 and 12 years. The skin testing was done by the scratch method. In this group, there were 218 positive skin tests to food. Of these, only forty-four (20 per cent) were shown to be of etiological significance. Egg white, fish, peanut, walnut, and chocolate accounted for thirty-eight of the forty-four significantly positive tests. Twenty-four of the 100 children were known to develop asthma following the ingestion of certain foods. It was of some practical importance that in the majority of cases their mothers had been aware of this before any skin testing had been done. Positive scratch tests to 158 foods, 72 per cent of all tests done, were shown to be of no clinical significance. Twenty-two positive tests to potato were observed, but in no instance could it be shown that ingestion of potato produced bronchial asthma or any other symptom.

Hill's findings are supported by the observations of Adams,³ who found that of 130 positive scratch tests to food only, 23 per cent were of clinical importance. Likewise, Chobot and Hurwitz⁴ reported that in their studies 18 per cent of 198 positive scratch tests to food were of clinical significance.

Hill² concludes that "about a fifth of positive scratch tests to foods in asthmatic children are of etiologic significance" and that "sensitivity to food, which should always be taken into consideration in asthmatic children, is of relatively little importance in comparison with sensitivity to pollen, other

environmental allergens, and upper respiratory infections." Positive tests that were of etiological significance when the child was younger gradually become less so as the child grows older and gains increasing tolerance to foods.

In the light of these findings, it seems clear that persistence of cutaneous sensitivity to ingesta may lead to erroneous interpretation of skin tests and thereby to unnecessary and undesirable dietary restriction of the allergic child.

RUSSELL J. BLATTNER

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SAMUEL McCLINTOCK HAMILL

1864—1948

Samuel McClintock Hamill died at his home in Philadelphia on May 3, 1948. He would have been 84 years of age next November. His death marks the passing of one of the finest characters who influenced the course and ideals of American pediatrics during the first four decades of this century.

During his early professional years he was an instructor at the University of Pennsylvania from which he was graduated in 1888, and from 1901 to 1919 he was professor of pediatrics at the Philadelphia Polielinie.

Early in his career he became interested in child health, and it was in this field of pediatrics that he made his important contribution. In 1915-1916 he was president of the American Association for the Study and Prevention of Infant Mortality, and later, when this organization finally emerged as the American Child Health Association, he served again as president from 1931 to 1935. In 1929 he retired from practice and from then on gave all of his time and interest to child health work. As chairman of the Section on Medical Service of the Third White House Conference in 1929, he led and inspired a large group of pediatricians and scientists in other fields in producing a monumental study and report which included all aspects of child health. Urged by the Pennsylvania State Medical Society and the Governor of the state he took the chairmanship of the Emergency Child Health Committee for Pennsylvania, and in recognition of his work in this capacity the state society presented him with an award for distinguished service. He was also given a medal by the Philadelphia Pediatric Society "for notable service and achievement in child health."

He was chairman of the Section on Diseases of Children of the A. M. A. in 1911, and president of the American Pediatric Society 1913-1914. He was a founder member of the American Academy of Pediatrics and president in 1932. In 1940 the University of Pennsylvania conferred on him the honorary degree of Doctor of Science.

Dr. Hamill started his pediatric work as a practitioner giving his services to a few children and ended a distinguished career by giving them to all children in his community, his state, and in the nation. As he grew older and less active he never lost interest in pediatric affairs. When I visited with him at his home last November his mind was clear and active, and he was intensely interested in talking about current pediatric problems and developments. This was shortly before the death of Mrs. Hamill to whom he was married in 1895.

He had a closer relationship with the younger pediatricians during his life than any of the other men of his own generation. He told me once that when he was a young man he asked Dr. Jacobi how he always kept so young in spirit and in his interests, and Dr. Jacobi told him it was because he had always kept close to the younger men. Dr. Hamill took this advice to heart, and this was one of the reasons "Sam" was so loved and respected and looked up to by the group some twenty years younger. He inspired us and gave us leadership and we looked upon him as our friend and companion without the thought of age.

B. S. V.

News and Notes



This photograph of Dr. Henry Helmholtz, Chief Medical Consultant for Europe for the United Nations International Children's Emergency Fund, was taken in Vienna while he was visiting a school in the Russian zone. Many will recognize Mrs. Helmholtz in the background.

Book Reviews

Child Care: Questions and Answers. Children's Welfare Federation, New York, N. Y., 1948, Doubleday & Company, Inc., pp. 159. Price \$2.00.

This book was prepared by a special committee of the Children's Welfare Federation of New York. Workers from the 200-odd members of the Federation submitted questions asked by parents of children from birth to 6 years of age. A special committee then selected the most frequent and important questions and in this text answers them. It covers the fields of growth, feeding, routine care, development, emotional guidance, medical care, and the special senses. The answers are clear, simply written, and in keeping with the best of present-day pediatric thought. It is by far the best text along this line we have encountered. The book should be of great value and help to workers in children's clinics and centers, to teachers in nursery schools, and to all lay individuals who are in some way responsible for the care of young children.

Editor's Column

THE EDITORIAL CONTROL AND POLICIES OF THE JOURNAL

In the July issue a year ago we discussed certain plans to make THE JOURNAL OF PEDIATRICS of more practical value to the man in practice. While continuing the publication of clinical and laboratory studies upon which progress depends, opportunity was afforded last year to develop the JOURNAL at the same time in a way which would make it of greater value and interest to the practitioner who is responsible for the direct care of children, whether he be a pediatrician or general practitioner. Despite a necessary increase in subscription rates due to the tremendous increase in the cost of paper and printing, the JOURNAL now has to print a thousand more copies each month than it did in the first half of 1947.

During the year a new Editorial Board, whose names appear on the cover, was appointed. The membership is made up of representative pediatricians who hold the same feeling and attitude to the desirability of the proposed changes as the Editor.

By formal agreement entered into between the Editor and Editorial Board, and the publishers, the Editorial Board has entire control of the editorial policies of the JOURNAL. That there may be no misunderstandings the Editor would like to state that the publishers have never once interfered with or made suggestions as to the editorial policies of the JOURNAL since it was started in July, 1932.

The Editorial Board is thus in entire editorial control of the JOURNAL. It is a self-perpetuating board with power to fill vacancies and to add additional members if it is deemed in the best interests of the JOURNAL. Further, the selection of the Editor is the responsibility of the Board.

The publishers have voluntarily proposed to limit the amount of paid advertising carried by the JOURNAL, and that nothing shall be advertised unless it is acceptable to the Board.

Editorially the JOURNAL will continue to discuss pediatric matters and problems, and the views expressed will represent the views of the Editorial Board, or of individuals signing editorials if approved by the Board for publication.

As Editor we take pleasure in presenting this statement as to the editorial control of the JOURNAL.

BORDEN S. VEEDER.

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Original Communications

ANTIBODY FORMATION IN EARLY INFANCY AGAINST DIPHTHERIA AND TETANUS TOXOIDS

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THE belief that there is a striking defect in the ability of young infants to produce specific antibodies has been rather widely held and has been the basis for the practice of deferring active immunization until later infancy. The present paper is the report of a study made on a group of infants to determine their ability to produce specific antibodies against two antigens, diphtheria and tetanus, antitoxins of which can be more or less accurately determined quantitatively and are generally accepted to be associated with clinical immunity.

METHOD OF STUDY

The infants tested were healthy babies in attendance at the Health Centers at Washington University Pediatric Clinic and at one of the St. Louis City Health Clinics and included both white and Negro children. Their ages varied from 1 to 14 months, although most subjects were under 6 months of age. At the first visit, blood was drawn, tested for diphtheria and tetanus antitoxins, and a subcutaneous injection of combined diphtheria and tetanus toxoid* given. A second injection of the same material was given two months later, and one month after this second injection a blood sample was again titrated for diphtheria and tetanus antitoxin. No unusual local or general reactions followed the injections. Schick tests were performed on all babies after the immunization, but so few of the children returned for the readings that no analysis of the results could be made.

RESULTS

Tetanus.—In a total of 284 infants from 1 to 14 months of age tested before immunization, none had detectable tetanus antitoxin in the blood. All had

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*The toxoid antigen used was combined Diphtheria-Tetanus Toxoids Alhydrox (Cutter), and the dose given was one cubic centimeter. The material was furnished by the Cutter Laboratories, and all antitoxin titrations using the standard guinea pig method were done by the Cutter Laboratories, Berkeley, Calif., under the direction of Mr. R. B. Clark, Supervisor of Clinical Research.

less than 0.01 unit per cubic centimeter, the smallest amount detectable by the method used. The results of tests one month after the second injection of toxoid in 188 infants are shown in Table I. It will be noted that 181 showed one unit or more of antitoxin per cubic centimeter. Five of the 127 in whom the immunization was started before the age of 6 months showed between 0.3 and 1.0 unit, while only two babies, both over 6 months of age, showed as little as 0.01 to 0.1 unit of antitoxin.

TABLE I. RESULTS OF IMMUNIZATION WITH TETANUS TOXOID IN 188 INFANTS

AGE AT FIRST TOXOID INJECTION (MO.)	NUMBER IMMUNIZED	ANTITOXIN TITER AFTER IMMUNIZATION, UNITS PER CUBIC CENTIMETER		
		0.01 TO 0.1	0.3 TO 1	1 OR MORE
1 to 3	73		4	69
3 to 6	54			53
6 to 14	61	2	1	59
Total	188	2	5	181

These results show that the mechanism for producing antibodies, as judged by the response to tetanus antigens, is well developed even in early infancy, since more than 95 per cent of those first inoculated from 1 to 6 months of age developed an excellent immunity, and in the remainder the antibody response was very good. Indeed in only two, or a little more than one per cent of 188 infants immunized, could the response be considered inadequate.

TABLE II. DIPHTHERIA ANTITOXIN FOUND IN 284 NORMAL INFANTS

AGE (MO.)	NUMBER TESTED	DIPHTHERIA ANTITOXIN TITER, UNITS PER CUBIC CENTIMETER			
		LESS THAN 0.03	0.03 TO 0.1	0.1 TO 1.0	1.0 OR MORE
1 to 3	112	75 (67 %)	9	18	10
3 to 6	90	74 (82.2%)	8	6	2
6 to 14	82	79 (96.3%)	0	2	1
Total		228 (80.3%)			

Diphtheria.—Of 284 infants from 1 to 14 months old tested for diphtheria antitoxin before immunization, 228, or 80 per cent, had less than 0.03 unit of antitoxin per cubic centimeter. However, as was to be expected, the proportion of those with demonstrable passive immunity varied considerably with the age of the baby, as shown in Table II. Here it will be noted that of those under 3 months of age, about one-third had antitoxin, while of those from 3 to 6 months old less than one-fifth had a passive immunity, and in the babies over 6 months less than 4 per cent had antitoxin. The number of infants in the early months of life who had a passive diphtheria immunity inherited from their mothers was somewhat less than in studies reported previously, and the possible reasons for this will be discussed later.

After immunization, 191 of the infants were tested. A summary of the results is shown in Table III. Those who showed more than 0.1 unit of antitoxin per cubic centimeter were considered to have developed a definite immunity. It will be noted that in the group of seventy-five infants under 3 months of age, one-third failed to reach a titer of 0.1 unit or more while of those

TABLE III. RESULTS OF DIPHTHERIA IMMUNIZATION IN 191 INFANTS

AGE (MO.)	NUMBER TESTED	ANTITOXIN TITER AFTER IMMUNIZATION, UNITS PER CUBIC CENTIMETER				
		LESS THAN 0.03	0.03 TO 0.1	0.1 TO 1.0	1.0 OR MORE	PER CENT WITH 0.1 UNIT OR MORE
1 to 3	75	17	8	17	33	66.6
3 to 6	56	4	2	12	38	89.3
6 to 14	60	1	2	13	44	95.0
Total	191	22	12	42	115	82.2

from 3 to 6 months almost 90 per cent, and of those over 6 months, 95 per cent had developed immunity.

The relation of the presence of passive antitoxin in the blood and resistance to immunization in younger infants in this group was analyzed. In Table IV, are shown the results of immunization of 158 infants who showed less than 0.03 unit of antitoxin before the toxoid injections. It will be seen that even in the younger infants under 3 months of age, 83 per cent developed immunity, although the figures of 87 per cent in those 3 to 6 months old and 95 per cent in the age group over 6 months are definitely better.

TABLE IV. DIPHTHERIA IMMUNIZATION IN 158 INFANTS WITH NO PASSIVE IMMUNITY

AGE (MO.)	NUMBER TESTED	ANTITOXIN TITER AFTER IMMUNIZATION, UNITS PER CUBIC CENTIMETER				
		LESS THAN 0.03	0.03 TO 0.1	0.1 TO 1.0	1.0 OR MORE	PER CENT WITH 0.1 OR MORE
1 to 3	52	7	2	12	31	82.7
3 to 6	46	4	1	7	34	87.0
6 to 14	60	1	2	13	44	95.0

The results of immunization of thirty-three babies in whom antitoxin was present before immunization are shown in Table V. When attempting to determine the development of an active antitoxic immunity in a group of infants who already have a passive antitoxic immunity, the interpretation of the results depends upon whether or not the titer has risen after the immunization. In most of the infants studied the antitoxin titer was lower after the toxoid injections than before. The striking defect in active antitoxin formation is shown by the fact that less than one-third of the infants under 3 months of age had more than 0.1 unit of antitoxin per cubic centimeter, whereas almost 83 per cent had had such a titer before immunization. In a review of the individual infants no constant quantitative relationship was found between the amount of passive antitoxin present and the inability to develop an active immunity,

TABLE V. DIPHTHERIA IMMUNIZATION IN 33 INFANTS WITH PASSIVE IMMUNITY

AGE (MO.)	NUMBER TESTED	DIPHTHERIA ANTITOXIN TITER IN UNITS PER CUBIC CENTIMETER							
		BEFORE IMMUNIZATION			AFTER IMMUNIZATION				
		0.03 TO 0.1	0.1 TO 1.0	1.0 OR MORE	LESS THAN 0.03	0.03 TO 0.1	0.1 TO 1.0	1.0 OR MORE	PER CENT WITH 0.1 OR MORE
1 to 3	23	4	11	8	10	6	5*	2	30.4
3 to 6	10	4	4	2	0	1	5†	4	90.0

*Three of these were the same, and one was less than before immunization.

†Two of these were the same, and one was less than before immunization.

since some infants with the lowest titer (0.03 to 0.1 unit) had less than 0.03 unit when retested after immunization. While the result appeared better in the small group of infants 3 to 6 months old, it was true that in some of these in whom the antitoxin content appeared good, the titer was the same or slightly less after than before the toxoid was given, as was the case in the younger age group. Although the number of passively immune babies studied is relatively small, the results are so definite and striking as to leave little doubt as to their significance.

To summarize briefly, it was found that so far as tetanus antigen is concerned, the mechanism for the production of specific antibody (antitoxin) is apparently as good in early infancy as it is later, since practically all infants showed an excellent response. With diphtheria antigen, infants under 3 months of age responded to active immunization poorly, and this interference with antibody production was due to the presence of recognizable passive immunity in most instances. Even small amounts of demonstrable antitoxin may prevent the active immunity, and it seems possible that this fact may explain the decreased percentage of subjects in the 3-to-6-month age group who developed immunity. After the age of 6 months, good immunity developed in 95 per cent.

DISCUSSION

The long-held belief that young infants respond poorly to antigens has been accepted by most authorities and has been the reason for the general practice of deferring active immunization until the latter half of the first year. This has been supported by some observations in rabbits that young animals produce antibodies less well than older ones, and by the fact that many infections are more severe and fatal in the neonatal period and in the early months of life than later, although it has long been realized that immunity to vaccinia develops as readily in early infancy as later. The principal reason, however, is apparently derived from the views of Dr. William H. Park and his co-workers in their pioneer work with active immunization in children against diphtheria, which really formed the basis and pattern for much of the subsequent development of active immunization. The statement is made frequently in their papers that immunization should be deferred until after 6 months, and this conclusion was apparently reached from the following observation,¹ which is the only direct reference to the subject in their many reports:

"Two thousand infants were given full doses of toxin-antitoxin on the third, eighth, and eleventh days after birth. One year later 100 were tested, and 52 per cent gave negative Schick tests. Since untreated infants gave the same result, it was evident that the combined effect of the immature cells and the over-neutralization of the toxin-antitoxin present (because of the passive immunization derived from the mother) prevents any appreciable response to the toxin-antitoxin injections."

In diphtheria it has been generally accepted that passive immunity in early infancy as indicated by a negative Schick test interfered with active immunization, although the present paper reports the first time this has been demonstrated

by actual antitoxin determinations. This inhibition of active antigen stimulus by passive immunity is apparently identical with that which has been shown in artificial passive tetanus immunity,² and is apparently due to the fact that toxoid antigen combines with antitoxin, and the neutralized antigen cannot exert the usual antigenic stimulus.

The number of infants in the series here reported who had a passive immunity in the early months of life was only about 34 per cent, a figure which is less than half of that reported by Karasawa and Schick and by v. Gröer and Kassowitz in studies of more than thirty years ago. Because of these early reports the belief is still widely held that a considerable majority of young infants possess a high degree of immunity to diphtheria for some months after birth. It should be remembered, however, that in the days when most of such studies were made (1915-1922) diphtheria was relatively prevalent in the large cities from which statistics were collected, and the percentage of 65 to 72 per cent of natural immunes is no longer applicable to most populations. Even then the figures³ from rural and suburban districts where diphtheria was less common showed only 42 to 48 per cent of immunes. In recent times, Wright and Clark,⁴ in a study of 250 parturient women from suburban London, found 44 per cent had negative Schick tests, while Vogelsang and Kryvi⁵ in Bergen, Norway, found only 27 per cent of 500 such women to have negative Schick tests. It is apparent, therefore, that there is no justification for applying generally the results of the early surveys to modern populations, in whom the percentage of immunes is often less than in a previous generation because of differences in the incidence of the disease.

The possibility has been suggested that in the United States, where active diphtheria immunization is practiced on many children, a definite increase in antitoxin immunity might have developed and persisted to adult life. On the other hand, in the past decade the incidence of diphtheria has fallen, so that in the United States the mortality from the disease is now less than 5 per cent of what it was when most of the studies were made; thus it would be expected that the number of natural immunes would be considerably lower. This seems to be substantiated by the fact that in a group of 2,933 troops of the United States Army from widely scattered areas of the United States, 55 per cent had negative Schick tests.⁶ It must be concluded that from one-third to one-half of infants have a passive diphtheria immunity in the early months of life. This immunity persists in various infants up to 6 months, and while it is present, the infants are resistant to active immunization with diphtheria antigens. It would appear advisable, therefore, to defer active diphtheria immunization until after the sixth month since at this time the highest percentage of active immunes would be obtained.

The chief interest in immunizability of young infants and their immunity response mechanism, and the main reason for the present study, concerns the use of whooping cough antigens. Diphtheria and tetanus are at present such a slight hazard in early infancy that there appears no valid necessity for attempting early immunization. The well-known mortality of pertussis during the first year of life, however, has stimulated interest in the possibility of

immunization in the early months since no one questions the desirability of early active immunization against whooping cough if this is possible. The belief in the poor response to antigens by young infants has been so strong that it is the routine practice to give pertussis immunization only after the sixth month, although a few physicians have been attempting earlier injections. In a recent well-controlled field study, Sako⁷ has reported that he found early pertussis immunization as effective as that done in later infancy. The evidence presented in the present study shows conclusively that the mechanism for antibody formation against tetanus antigen is as well developed in early infancy as it is for vaccinia, and that only when a passive antibody is present as in certain cases of inherited diphtheria immunity is there an interference with antibody formation. If the ability to produce specific antibodies is well developed in early infancy, there appears no reason that antibodies to pertussis antigen cannot be as readily formed as those to tetanus antigen, and the justification for early pertussis immunization is strengthened.

Recently, there has been some tendency to use a routine of diphtheria, pertussis, and tetanus antigens by simultaneous injection. While such multiple antigens are as effective in immunization as those given individually, they would seem to be most useful when given to infants after 6 months of age. Since, for the reasons stated, there are definite advantages in immunizing against diphtheria later in infancy and against pertussis in the early months, the "timing" is bad for routine use of combined antigens. A course which appears to meet the requirements as discussed, and which has been in use in the Washington University Children's Clinic for the past year, is to give pertussis vaccine at the sixth, ninth, and twelfth weeks, and combined diphtheria and tetanus toxoids in the seventh and ninth months.

SUMMARY

A study was made of the development of antitoxin after two injections of combined diphtheria and tetanus toxoids in a group of young infants. It was found that the production of tetanus antitoxin is as good in the early months of life as later, and this finding denotes that the mechanism for the production of antibodies is well developed in young infants. With diphtheria antigen, the development of antitoxin is definitely defective in a considerable number during the first 6 months of life. This impairment of antibody formation is related to the presence of passive immunity in the resistant infants and appears specific for diphtheria. The application of these findings to the practical immunization of infants to diphtheria, tetanus, and whooping cough was discussed.

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GALACTOSEMIA

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GALACTOSEMIA, chronic hypergalactosemia, galactemia, and galactose diabetes are terms used to designate a metabolic disorder of infancy, characterized by the symptoms of failure to gain weight and grow properly, with the chief signs of hepatomegaly, splenomegaly, melituria, and albuminuria.

The first authentic case was reported by Göppert¹ in Germany in 1917. His patient was 2 years and 5 months of age when first observed. The child had had a history of jaundice for the first eight months of life, was poorly developed, malnourished, had a large liver, and there were albumin and sugar in the urine. The reducing substance was found to be galactose, and when milk was removed from the diet, sugar and albumin disappeared from the urine, the child gained weight, and the liver became smaller.

In 1935, Mason and Turner² published the first American report of a case in a Negro boy 6 months old who failed to gain normally as long as his diet contained milk, who showed marked enlargement of the liver and slight enlargement of the spleen and superficial lymph nodes, a positive van den Bergh, secondary anemia, osteoporosis, and albumin and sugar in the urine. The sugar was determined to be galactose. Removal of milk from the diet resulted in the disappearance of sugar and albumin from the urine, decrease in the size of the liver and spleen, improvement in the anemia and the osteoporosis, and disappearance of the positive van den Bergh with a rapid gain in weight.

Norman and Fashena³ in 1943 published the third case, in an 11-week-old white child, characterized by galactosuria, albuminuria, hepatosplenomegaly, mild azotemia, and osteoporosis. Removal of milk from the diet resulted in disappearance of all symptoms except the mild azotemia.

Mellinkoff and his associates⁴ in 1945 reported a similar patient, first seen at the age of 2 months, who in addition had evidence of liver damage as shown by a positive cephalin flocculation test. He also improved on a milk-free diet and had gained weight and appeared normal except for an enlarged liver at 7 months of age.

Bruck and Rapoport⁵ in the same year reported another case similar in all respects to the previous cases, in which there were, in addition, bilateral nuclear cataracts. All pathologic signs and symptoms including the cataracts disappeared when milk was removed from the diet. They also reported that cataracts were later discovered in Mason and Turner's patient.

The most recent article on galactosemia by Goldbloom and Brickman⁶ in July, 1946, reports two patients, aged 6 and 2½ months, with similar findings

¹From the Department of Pediatrics, Sinai Hospital, Baltimore, Md. Dr. A. J. Schaffer, Chief of Service.

including cataracts, who improved satisfactorily upon elimination of milk from the diet. The cataracts alone failed to clear.

There are several cases reported in the older literature in which galactose has been found in the urine, but because of other coexisting conditions they cannot be placed in the category of galactosemia.

We will report another case, bringing the total of the published cases to eight.

CASE REPORT

W. J., a white male infant, was admitted to the Children's Ward of the Sinai Hospital of Baltimore on May 28, 1947, at the age of $2\frac{1}{2}$ months, with a chief complaint of vomiting and diarrhea since birth.

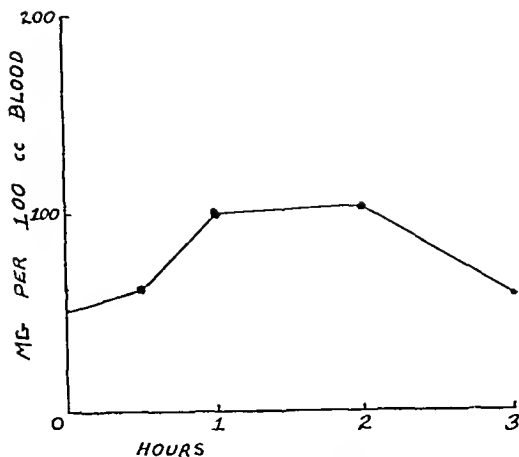
Family History.—The parents were both 35 years old and in good health. There were two siblings, aged 18 and 20 years, both living and well. The mother had had one abortion in the first trimester, cause unknown. A maternal grandmother was a known diabetic.

Past History.—The child was born at term and delivery was uneventful. The birth weight was 8 pounds. He became jaundiced on the third day of life and remained so for one week.

Present Illness.—From the age of 2 weeks the child began to vomit his feedings, requiring frequent changes of formula.

At one month of age he developed coryza with cough, and at that time he developed a diarrhea lasting two days. He was treated with one injection of penicillin. Following this he had a constant cough, sneezing, and associated sweating and pallor. There were alternating vomiting, diarrhea, and constipation. One week prior to admission his stools became greenish in color and mucus was noted on several occasions. The mother had noticed frequent swallowing of air, with eructation and flatulence. The child was noted to ruminate after regurgitation of food. He always seemed hungry, and he lost weight. He was seen by Dr. Askin on the day of admission, who found an enlarged liver and recommended hospitalization for investigation with a working diagnosis of von Gierke's disease.

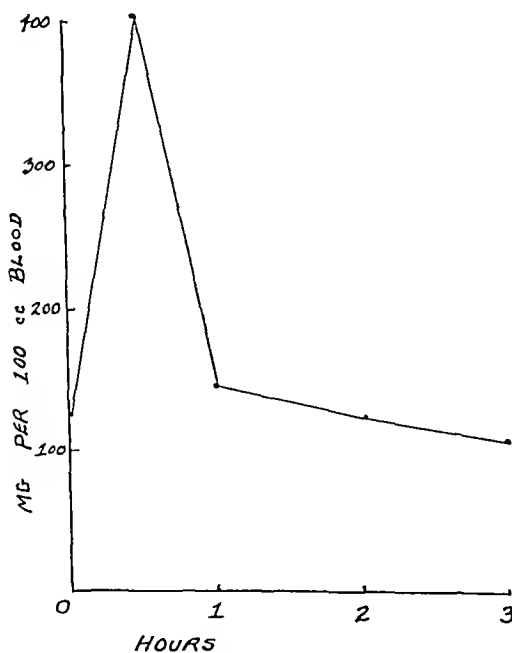
Physical Examination.—The temperature was 100° F., pulse 140, respiration 26, weight 7 pounds, $5\frac{1}{2}$ ounces, head 38 cm., chest $30\frac{1}{2}$ cm., length 59 cm. Examination revealed a small, poorly nourished, pale, $2\frac{1}{2}$ -month-old white male infant, who appeared acutely ill. He was alert and his cry was vigorous. Bilateral zonular cataracts were observed. The abdomen was protuberant. The liver was smooth, enlarged, and firm, the edge reaching three fingers below the costal margin. Laboratory findings were as follows: STS and tuberculin tests were negative; the red blood count was 3.11 million, hemoglobin 8.0 Gm., white blood count 25,300, with 58 per cent polymorphonuclear cells. The original urine showed a 2 to 3 plus albumin; it was negative for sugar and acetone. Several morning urine specimens revealed no sugar, but on the fourth day a specimen taken a short time after feeding revealed a one plus sugar. Thereafter, repeated urinalyses revealed varying amounts of sugar from a trace to 4 plus by the qualitative Benedict's test, and albumin from a trace to 2 plus by the heat and acetic acid test. The fasting blood sugar (venous blood) was 79 mg. per cent, cholesterol 192 mg. per cent, calcium 11 mg. per cent, total protein 5.5 Gm. per cent, albumin-globulin ratio 3.8/1.5. The bilirubin was 7.0 mg. per cent. The direct van den Bergh was 1.1 mg. per cent. The thymol turbidity was 4.7 units; the alkaline phosphatase was 8.4 units; the bromsulphalein revealed no retention in thirty minutes. The PSP test showed 90 per cent excretion in three hours. The prothrombin time was thirty-seven seconds, with a control of thirty seconds. The x-ray of the chest was negative. A roentgen examination of the abdomen revealed "intestine displaced to the left and downward by a mass, probably an enlarged liver; the long bones were not remarkable." The presence of a reducing substance and albumin in the urine, associated with retardation in growth and development, cataracts, and an enlarged liver, suggested the condition of galactosemia.



MAY 29, 1977

FIG. 1

Fig. 1.—Total blood sugar values after the ingestion of 1.75 Gm. of glucose per kilogram of body weight.



JULY 31, 1977

FIG. 2

Fig. 2.—Total blood sugar values after the ingestion of 1.75 Gm. of galactose per kilogram of body weight.

Identification of the sugar in the urine was then undertaken. Fermentation with baker's yeast was shown to be negative. Osazone crystals were prepared, which could not be distinguished from galactosazone. Mucic acid crystals were obtained, identical with those obtained with galactose. The phloroglucinol test was reported as equivocal. The reducing substance in the urine was thereby identified as galactose. A glucose tolerance test was done and a normal curve obtained. An oral galactose tolerance curve was also done. The blood sugar rose to 400 mg per cent one half hour after the ingestion of 1.75 Gm. of galactose per kilogram (See Figs 1 and 2)

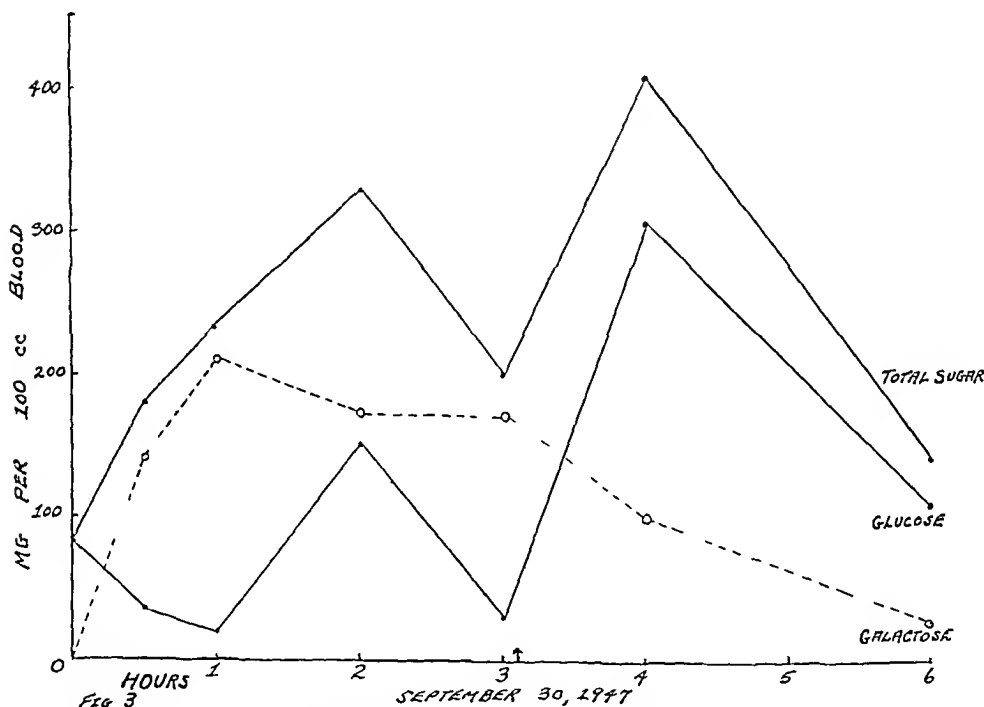


Fig 3—Values for total blood sugar, glucose and galactose after the ingestion of 1.75 Gm of galactose per kilogram of body weight

Course in Hospital—On the basis of identification of urinary sugar as galactose and an abnormal galactose tolerance curve, a diagnosis of galactosemia was made and the child put on a milk free diet. A Nutramigen and cane sugar formula was substituted for milk. On this regime the urine became free of albumin and the reducing substance. The child began to gain weight, increasing from 7 pounds, 8½ ounces on admission to 9 pounds, 10½ ounces on discharge nine and one half weeks later. The liver was somewhat smaller at the time of discharge, and the vomiting had ceased. The child was discharged to return later for further study.

He was readmitted on Sept 28, 1947, at the age of 6½ months, seven weeks after discharge, during which time he had gained three pounds, 7 ounces. Physical examination revealed a well nourished, fairly well developed white male child, alert and active. The cataracts had completely disappeared. The abdomen was full, and the liver edge was palpable 3 fingerbreadths below the costal margin. Laboratory studies revealed the following: The red blood count was 3.4 million, the hemoglobin 8.4 Gm, the white blood count was

*We are indebted to Dr Harold Harrison of Baltimore City Hospitals for aid in identification of the urinary sugar

11,100 with 27 per cent polymorphonuclear cells and 73 per cent lymphocytes. The urine was negative for albumin, sugar, and formed elements. The urea was 16 mg. per cent, the fasting blood sugar 68 mg. per cent. The total proteins were 6 Gm. per cent, the albumin-globulin ratio was 4.5/1.5, and the van den Bergh was negative. The cholesterol was 148 mg. per cent, with 58 per cent esters. The calcium was 11.4 mg. per cent and the phosphorus, 4.5 mg. per cent. The carbon dioxide combining power was 41.2 volumes per cent. A glucose tolerance test was done. After the ingestion of 1.75 Gm. of glucose per kilogram, a normal or slightly flattened curve was obtained. A galactose tolerance curve after the ingestion of 1.75 Gm. of galactose per kilogram showed a high rise in one hour and a reduction to almost fasting level in six hours. Depression of the glucose level coincident with the rise of blood galactose was shown. During this test, 7.81 Gm. of galactose was excreted in the urine. On one occasion the glucose (blood) fell to 19 and on another to 8, without evidence of shock. (See Figs. 3 and 4.)

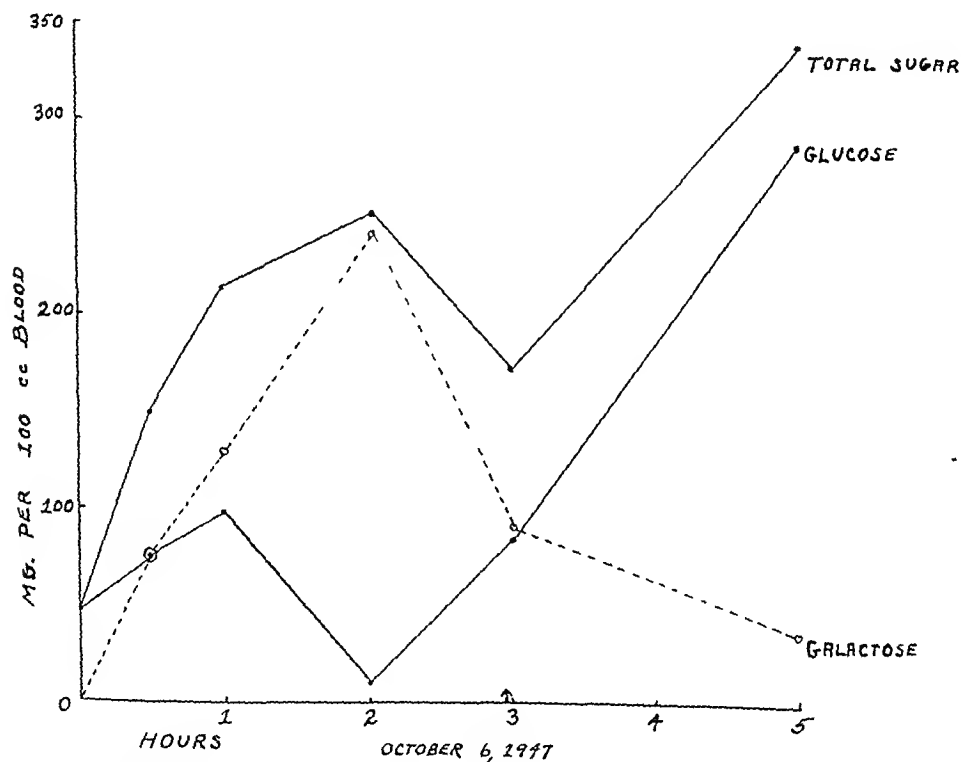


FIG 4

Fig. 4.—Values for total blood sugar, glucose, and galactose after the ingestion of 1.75 Gm. of galactose per kilogram of body weight.

COMMENT

Another case of galactosemia is reported. Our patient was characterized by failure to gain weight and grow properly, general underdevelopment, enlargement of the liver, melituria (galactose) albuminuria, anemia, and cataracts. Removal of galactose from the diet resulted in improvement of all abnormalities except for hepatomegaly, which showed but slight change. Our case differs but little from those previously described.

In several of the cases reported, careful studies have been made on carbohydrate metabolism, which we have attempted to duplicate. From these studies the following conclusions may be drawn: (1) There is a normal glucose tolerance curve. (2) There is an abnormally high galactose tolerance curve. (3) The two sugars, glucose and galactose, have mutually antagonistic effects upon one another. Attempts to explain the pathologic changes occurring in this condition have been made by several workers. Mason and Turner feel that the primary trouble is a lesion or functional disturbance of the liver that lowers



Fig. 5.

Fig. 6.

Fig. 5.—W. J., aged 3½ months, before therapy.

Fig. 6.—W. J., aged 6½ months, after three months of milk-free diet

the ability of the organ to convert galactose into glycogen without seriously impairing the other functions of the liver. Milk in the diet results in galactose reaching the general circulation; the circulating galactose maintains the total blood sugar at a level high enough to stimulate the mechanism for lowering the blood sugar, and this mechanism, unable to act satisfactorily on the galac-

tose, acts excessively on the dextrose and causes the storage of abnormally large amounts in the liver. When milk is withdrawn from the diet, galactose disappears from the blood; the level of the blood dextrose again rises, and gradually the excess of stored glycogen is discharged from the liver." This explanation depends on the validity of the assumption that it is the height of the total blood sugar and not that of dextrose alone which sets in motion the mechanism for lowering the amount of blood sugar.

These same authors believe the other findings, such as anemia, osteoporosis, and elevated van den Bergh, are secondary, not primary, and in some way related to the continuous presence of galactose in the circulation. This they explain by (1) the diffusion of galactose throughout the body and its interference in some way with normal metabolism, or (2) a relative dextrose starvation, interfering with normal cellular activity. The albuminuria, they feel, is similar to that found in diabetic children when first observed, and which also disappears when they become sugar-free as the result of treatment.

Bruck and Rapoport raise several objections to Mason and Turner's hypothesis: first, that hypoglycemia per se, as seen in glycogen storage disease and hyperinsulinism, does not produce symptoms similar to those of galactosemia; and second, that hypoglycemia does not appear to be an essential feature of the disease. In their patient and in others the hypoglycemia was only transient, occurring only during a galactose tolerance test.

Bruck and Rapoport suggest a toxic effect of galactose on the various tissues as a cause of the pathologic changes noted in this disease.

Norman and Fashena agree with Mason and Turner that galactosemia is due to failure of the body to convert galactose into glycogen and that the associated manifestations are due to a relative dextrose starvation.

Mellinkoff feels the defect is due to galactose or a polymer of galactose being stored in the liver and causing injury to the liver with resulting hepatic dysfunction.

Most recently Goldbloom and Brickman suggest that the high blood level of galactose interferes with the absorption of glucose from the intestine and this causes the low blood glucose when lactose is being fed.

The presence of cataracts associated with this condition and the reversibility in some cases is of interest. In 1935, Mitchell and Dodge, in experiments on the effects of high carbohydrate diets, found that on diets containing 70 per cent of lactose, rats regularly developed cataracts, whereas equal amounts of starch, maltose, dextrin, or sucrose had no such effect. Subsequently it was proved that galactose, not lactose per se, was the offending compound. In some of the rats in which the lesion did not progress to the stage of complete opacity, the lens became completely clear.

SUMMARY

1. Another case of galactosemia, in a 2½ month old infant, has been reported and the literature reviewed.

Our case had the features common to all the other cases—namely, failure to gain weight and develop properly, melituria, and albuminuria. In addition,

our patient showed cataracts, which have been described in 50 per cent of the other cases. The reducing substance was identified as galactose. By the removal of lactose from the diet, there was subsidence of all the pathologic signs and symptoms except for the enlarged liver.

2. Carbohydrate studies were done, and results similar to those of previous workers were reached; these were a normal glucose tolerance curve, a high galactose tolerance curve, and antagonistic effects of glucose and galactose upon one another.

3. Theories of the mechanism of galactosemia have been reviewed.

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A STUDY OF PHYSICAL ACTIVITY IN JUVENILE DIABETIC PATIENTS

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EXERCISE was known to be an important factor in the treatment of diabetes mellitus long before the discovery of insulin. Since the discovery of insulin and the advances made in its refinement and modification, along with the recent rapid advances in our knowledge of nutrition, exercise as a factor in the treatment of diabetic patients has received little attention. The objective of our clinic in the management of diabetes mellitus is to maintain normal physiologic conditions. In most clinics the diabetic child is permitted to maintain a mild glycosuria as an insurance against shock. In this clinic, however, this state would be considered a level of only fair control. When the level of control requires that the child remain aglycosuric, the effects of exercise become more apparent.

In 1940 the method was described by this clinic for stabilization of children with diabetes mellitus.¹ The regimen outlined has been effective, and a large number of children have been able to maintain excellent regulation over extended periods of time. The importance of physical activity as a factor in maintaining stability became more apparent as the children were observed under home management. During vacation periods with greatly increased physical activity, insulin reactions occurred unless the insulin dosage was reduced or the food intake increased. Earlier, the families were advised to decrease the insulin. This resulted in less than expected weight gains during periods of the year when physical activity was strenuous. Histories obtained from the families revealed that insulin reactions were frequently associated with periods of excessive physical activity. Marked reduction of insulin requirement was common during the summer months or during periods of heavy work. A few children were able to maintain regulation for periods of time without the use of insulin. Soon it became obvious that it was better to give additional food rather than to decrease the amount of insulin in order to compensate for increased physical activity. The families were instructed to note variations in physical activity in their daily record books. They were advised to give small additions of food at meals or at the time of exercise. Clinically, the children were observed to maintain better regulation when the food was given at mealtimes. A graphic chart has been made for each diabetic child in our clinic from the home records kept by the families. These records include insulin requirement, growth, dietary intake, glycosuria, insulin reactions, infections, major emotional disturbances, and variations in physical activity. These records have been carefully studied to learn more about exercise as a factor in diabetic regulation of children.

This report on physical activity of diabetic children comprises two sections: (1) the effect of short periods of physical activity of children observed under experimental conditions, and (2) the effect of free activity of children observed in the outpatient clinic.

SECTION 1: ACTIVITY UNDER EXPERIMENTAL CONDITIONS

In 1941, as part of the requirement for a master of science degree, a graduate student of nutrition studied the effect of physical activity on the blood sugar values of diabetics under various levels of diabetic control during a one-hour experimental period.²

Method of Study.—The group was composed of one normal child, seven hospitalized patients, and ten outclinic patients whose diabetes was under various levels of control. Blood sugar values were determined on these eighteen subjects, who ranged in age from 3 to 22 years.

The observation period of physical exercise was in the morning between 9:30 and 10:30 o'clock, three hours after the morning dosage of insulin and approximately two and one-half hours after breakfast. Three types of physical activity were studied. They were: strenuous—running or bicycling; moderate—walking, skipping, swinging, jumping rope intermittently, and playground activity; minimum—reading, sitting, and lying down.

Finger-tip blood* was drawn one-half hour before the physical activity observation period, immediately preceding it, at the mid-period, at the completion, and one-half hour after completion.

Findings.—The following is a brief summary of the findings as reported in the thesis:

Regardless of the type of activity the blood sugar values of the one normal child in the study group were within normal range. When her blood sugar values were over 100 mg. per 100 ml. at the beginning of the physical activity study period, the values all decreased for each of five moderate exercise periods with a mean change of -17.6 mg. per 100 ml.; when her blood sugar values were less than 100 mg. per 100 ml., her blood sugar values increased for each of two moderate exercise periods and decreased very slightly for one period with a mean change for the three periods of 11.3 mg. per 100 ml.

The three subjects in excellent diabetic control had blood sugar values which varied from 59 to 104 mg. per 100 ml. one-half hour before exercise and from 79 to 120 mg. per 100 ml. one-half hour after the completion of exercise. Six patients under good control were observed for a total of nine study periods. During or after minimum, moderate, and strenuous physical activity there were no marked fluctuations in the blood sugar values. (See Figs. 1 and 2.)

No significant alterations in blood sugar values were revealed after short periods of moderate exercise in patients when the disease was fairly well controlled. Patients under fair control who had elevated postprandial blood sugar levels had a progressive lowering of blood sugar values, but no rapid lowering.

*A micromodification of the Folin-Wu method was used for estimation of sugar content, and the Somogyi method for precipitation was employed.

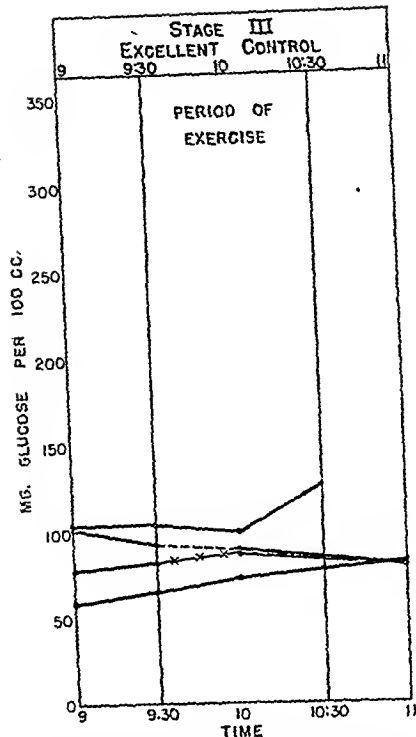


Fig. 1.—Blood sugar changes during and after the experimental period of physical activity from 9:30 to 10:30 A.M. of patients whose diabetes was under excellent control. The blood sugar values were not noticeably affected by the exercise. x x x indicates minimum degree of physical activity, — moderate, and - - - strenuous.

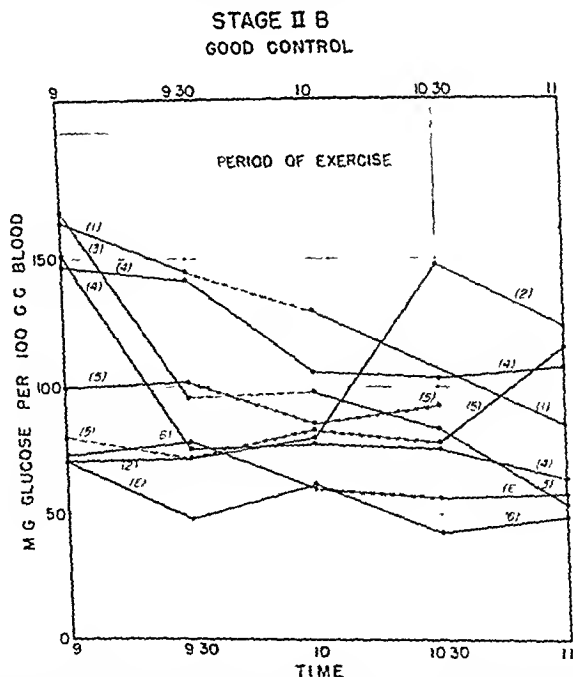


Fig. 2.—Blood sugar values at the beginning, during, at completion, and one-half hour after completion of the experimental period of physical activity of patients whose diabetes was under good control. (Symbols same as in Fig. 1.) The observations were made for six children for a total of nine experimental periods. An ascending curve during moderate activity was shown by patient (2), who was used to manual labor. Otherwise minimum, moderate, or strenuous physical activity caused no great variation in blood sugar values.

In all stages of management of children with diabetes mellitus, during or after short periods of moderate to strenuous physical exercise there tends, with few exceptions, to be a lowering of the blood sugar values. The greatest decrease in blood sugar values was for those who had elevated blood sugar values at the beginning of the observation period of physical activity.

During experimental exercise periods the blood sugar values of the stabilized diabetic children decreased gradually, and no child experienced an insulin reaction during the hour of exercise or immediately after it. This sample of seventeen diabetic subjects is small, but the consistency of the finding of a gradual lowering of the blood sugar value during increased exercise suggests that if a child has been stabilized and is maintaining a good level of diabetic control, he can compensate for short periods of unusual exercise ranging from moderate to strenuous by taking an amount of extra food at mealtimes commensurate with the increased need.

One patient in the stage of metabolic recovery was studied for two separate periods of moderate exercise. He was rapidly gaining weight, and his daily insulin requirement was decreasing. His blood sugar values were low, and during the experimental exercise periods he complained of weakness and had to rest before the end of one of the periods.

SECTION 2: FREE ACTIVITY

Type of Muscular Exercise Taken by Diabetic Children and Adolescents Living in Rural Communities.—The muscular exercise taken by the young diabetic children under the supervision of the clinic of Children's Hospital was for the most part determined by the child's inclinations and the circumstances of his home life and school program. The children were, however, instructed to participate in activities that would not conflict with the regularity of their diabetic regimen.

A number of children have been specific in recording in their daily record books the amount and kind of activity of consequence in which they participated over and above the routine of an ordinary day. Several boys particularly have been able to manage a great deal of activity without loss of diabetic control. One high school boy (R. G.) after school hours manages to practice basketball or band or orchestra or plays for dancing, and in the summertime has detasseled hybrid corn eight to nine hours a day. Another boy (R. S.), in junior high school, lists as his extra activities one to three hours of basketball practice, baseball, swimming, bicycle riding, boxing, mowing lawns, and working in a bowling alley three to four hours. A grade school girl (A. H.) carefully listed her extra activities. They included housework, shopping, sleigh-riding, baseball at recess, flower picking, parties, and playing in the snow. A high school girl (M.D.) listed her extra activities as housework, walking to town, gymnasium class, and social dancing in the evening. As a rule the children did not record so much specific detail as those just mentioned, but stated in general whether the exercise was usual, more, or less, for school or vacation time. This review, however, of the detailed records is helpful in evaluating the amount and strenuousness of

activity of some diabetic children and adolescents residing in rural or semirural areas. The inactivity also is recorded. Bed rest probably represents the least daytime activity. Many indicate inactivity as less than usual with the explanation of a rainy day or very cold day.

Constancy and Fluctuations in Exercise in Relation to Control of Juvenile Diabetes Mellitus.—In general the school routine tends to maintain the exercise of children at a fairly constant level from day to day during the school months. For a few diabetic children the variation in the amount of exercise for school days and for week ends is great enough to reflect itself and needs compensation. In the spring of the year when outdoor play and work start, for many the amount of exercise increases and is more variable from day to day. With the coming of vacation and still more activity, it has been observed that the well-regulated patient will have shocks unless some compensation is made. In the records there are instances of shock after periods of strenuous exercise such as swimming for a few hours and active play for a day at a picnic. There also are instances of shock after periods of gradually increasing exercise over a period of days such as the change from winter to spring farm work. Glycosuria invariably resulted when the amount of exercise was less than usual. These are typical reactions of patients who have not learned or have not heeded the advice to compensate for marked changes in exercise.

We have observed that some intrinsic characteristic of a few well-regulated patients makes them tolerate inconstancies in exercise better than average. For example, N. P., a girl whose diabetes has remained in excellent control, was able to exercise two days a week in her physical education classes without decreasing the amount of insulin or increasing the amount of food.

Illness can cause fluctuations in physical activity. The change from bed rest to usual activity has been observed to precipitate a shock when care is not used at this time to compensate for increased exercise.

Exercise in Relation to Age and Sex of the Diabetic Patient.—The age and sex of the child are factors to be considered in evaluating exercise. The games and play of children involve a great amount of physical exercise. The responsibility that the young child can assume to recognize the early signs of shock is at a minimum. The amount of reserve glycogen is relatively less than for the older child.

When boys and girls become adolescent the differences in strenuousness of the activity of the two sexes are accentuated. After puberty, girls tend to spend more of each day in less strenuous leisure, while the boys frequently spend more time in greater muscular activity, both in work and in leisure. The lack of exercise in many diabetic adolescent girls is a major factor for the rather frequent occurrence of obesity in this age group.

Compensation for Changes in Exercise.—The home records confirm the hospital experimental study that short periods of exercise, such as the intermittent exercise of a gymnasium class, of farm or household chores, or of walking, are tolerated by the well-regulated diabetic child. The basic diet, if adequate, will take care of minor fluctuations in daily exercise.

For an occasional period of very strenuous exercise, such as basketball practice for two hours or swimming vigorously off and on for two hours, some compensation should be made to avoid precipitating a shock. If a meal is to be eaten shortly after the exercise, extra food in proportion to the change in exercise should be given at this meal. If the exercise has been taken in the early evening, a lunch may be eaten during the evening or before going to bed.

If the child or young adult changes his whole pattern of exercise, as from school to vacation or from winter to spring farm work, the first adjustment in his regimen should be an increase in his basic diet commensurate with his increased physical activity. Earlier in our regulation of diabetic patients we lowered the insulin at times of prolonged increased activity. This method gave the apparent advantage of a lower insulin requirement, but it resulted in loss of body weight. C. V. illustrates this method of compensating for more exercise during vacation periods (Fig. 3). For three and one-half years this adolescent boy consistently kept an accurate home record of his insulin dosage. He reported that, because of increased activity at a summer camp in 1939, from mid-June to mid-August, he had to decrease considerably his insulin dosage to avoid insulin reactions. During the school months there was lessened activity necessitating a steady rise in insulin. During the spring months there was more activity, which was accompanied by a steady decrease in insulin need. During the first June spent at camp there were frequent mild insulin shocks associated with increased activity and a decided drop in insulin requirement, so that during mid-vacation he was able to decrease the daily insulin dosage by 27 to 32 units. Concurrently with this decrease in insulin, there was an increase of 187 calories in his diet and a weight loss of 7 pounds. The patient was usually aglycosuric, and only occasionally excreted a minimum amount of sugar in the urine. The glycosuria was usually associated with mild infections, which were immediately controlled. During a short spring vacation, in which activity was increased, there was a slight decrease in the insulin need. During the summer camp periods of 1940 and 1941 there were rapid decreases in the insulin requirement, but no shocks were recorded. The patient had learned from the experience in 1939 that increased activity reduced the insulin requirement.

C. H., a preschool child, also shows the influence of changing exercise on weight (Fig. 4). This little girl was inclined to a great deal of runabout play, and when the weather permitted she played practically the whole day outdoors except for her nap time. This accounts for her marked seasonal variations in exercise. Not until her basic diet was raised in the spring of the year did she make the expected weight gains. This condensed chart of her diabetic record reflects changing insulin requirements with seasonal variations in physical activity and with fairly frequent upper respiratory infections, so common to this age period. C. H. was treated early, her disease was moderately severe, her diabetic regulation was excellent, and she had a good tolerance of exercise. This child did not experience clinically significant shock, but on two occasions when her daily exercise was increasing, mild symptoms of shock were present and compensation was immediately made.

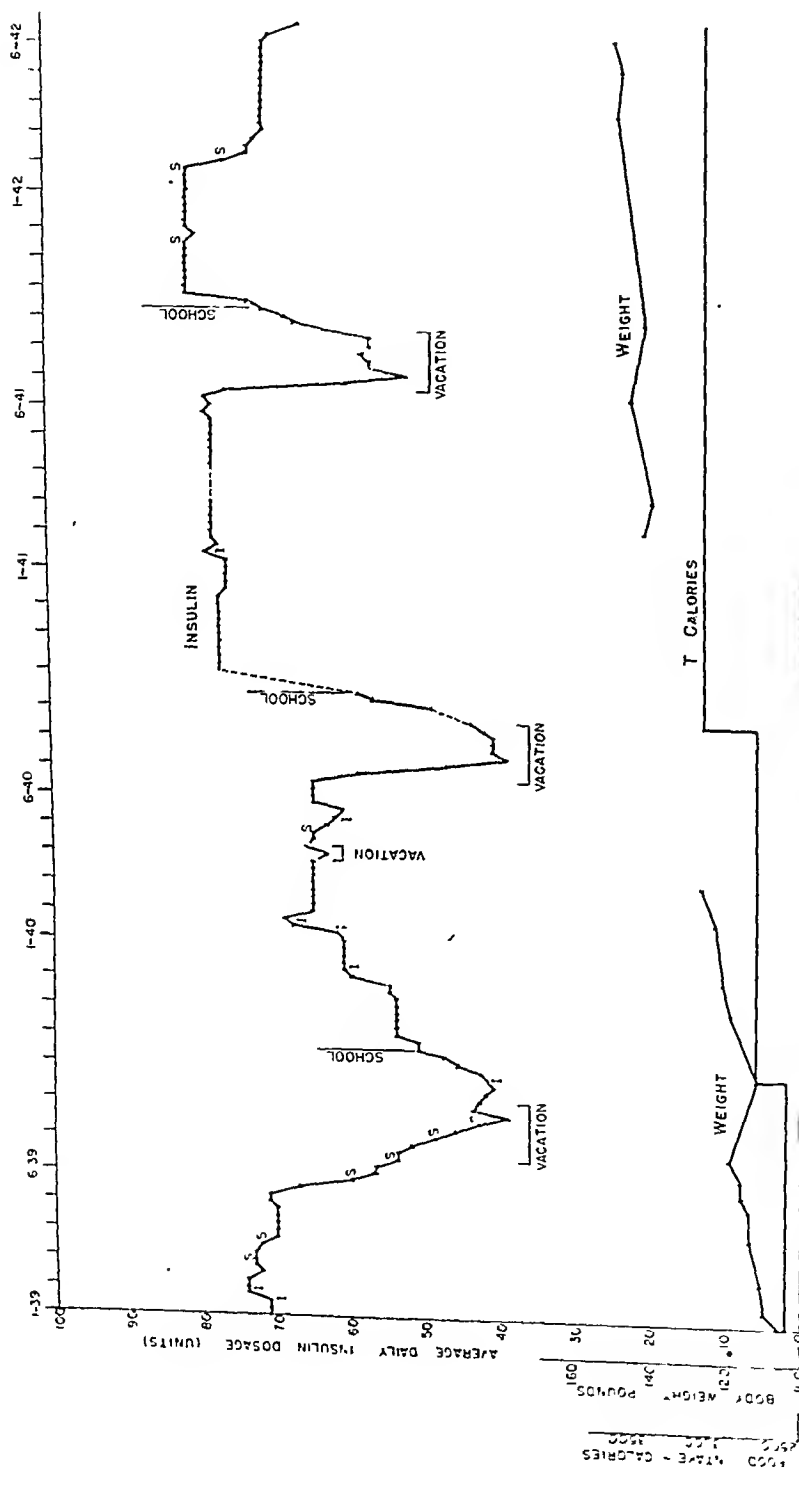


Fig. 3.—Daily insulin dosage of a boy, C. V., whose diabetes was under good control over a three and one-half year period, including school years and vacations, spent at a boy's camp. Regular exercise taken over a period of days and weeks resulted in a decided decrease in the insulin requirement. Return to school and the sedentary life necessitated sharp increases in insulin dosage. (I) represents an infection, which is usually followed by increased insulin dosage. (S) represents shock, which usually accompanied increased exercise and necessitated a decrease in insulin dosage. Weight loss was concurrent with increased activity without an increase in basic diet or extra food. The dotted line (---) represents the period in which data were not obtainable.

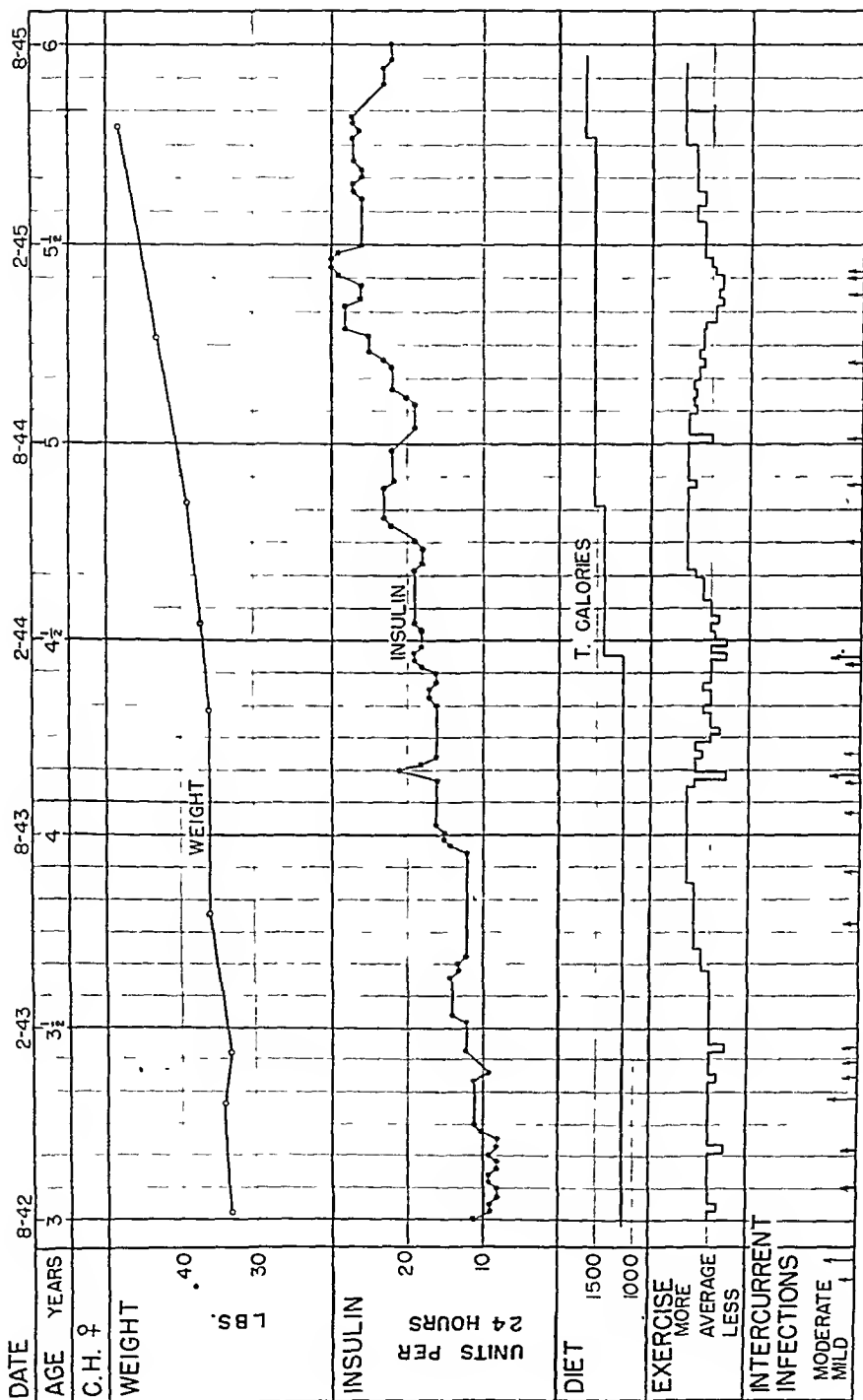


Fig. 1.—Shows three years of diabetic regulation under home conditions of a preschool girl, C. H., under excellent diabetic control. Her urine was free from sugar except for very occasional traces. There were no clinically significant insulin reactions, but on two occasions she had mild symptoms of shock with increased exercise.

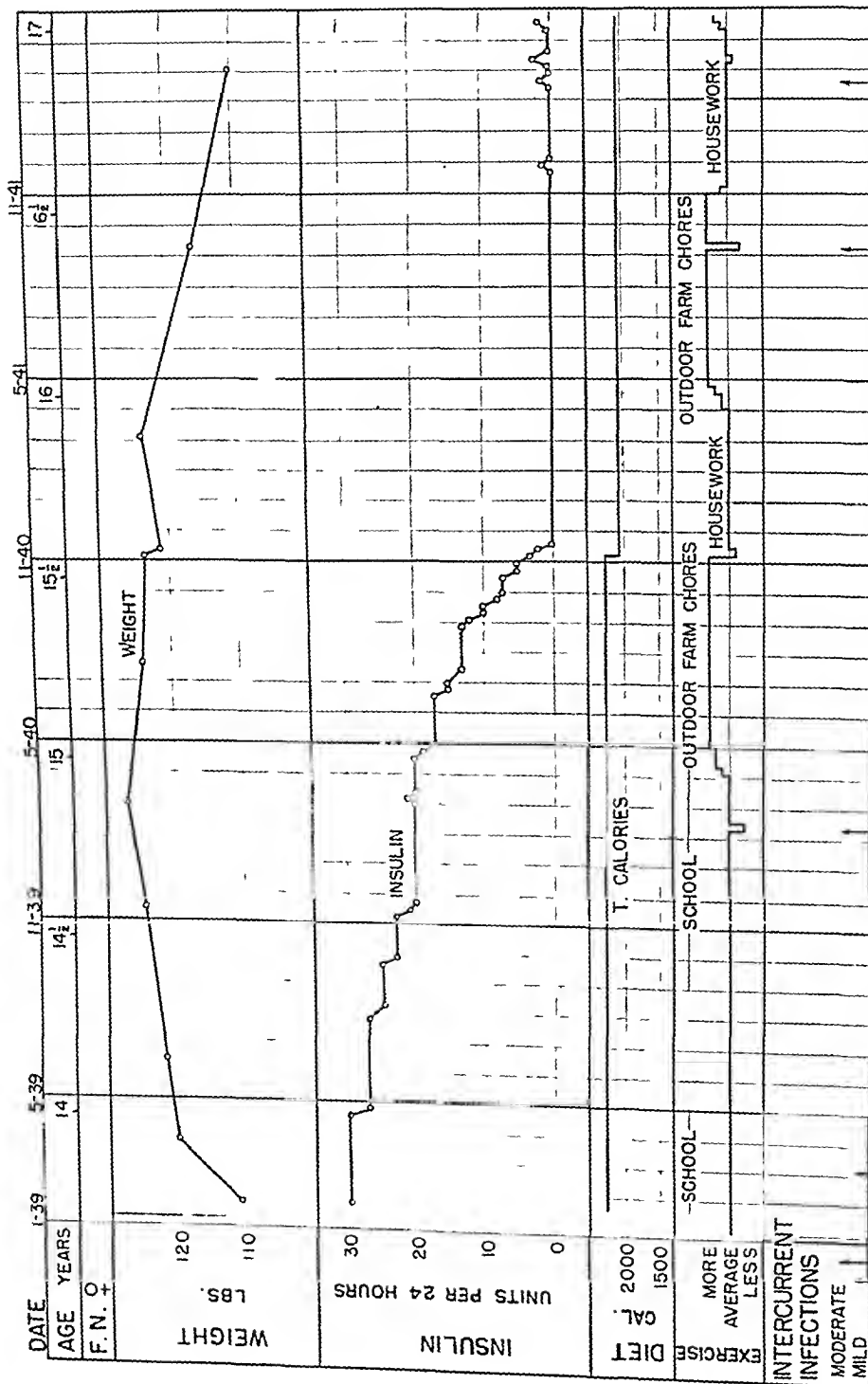


FIG. 5.—Shows three and a quarter years of diabetic regulation of F. N., a girl 13 years and 8 months of age at onset of the disease. Her diabetes mellitus was brought under excellent control shortly after onset, and at the time of her dismissal from the hospital she was taking 30 units of insulin daily. The course of her insulin requirement and weight changes in relation to her dietary, physical activity, and infections are presented.

F. N., a 13-year-old girl, had good health up to three weeks prior to her admission to the hospital (Fig. 5). At that time she had a cold, polyuria, polydipsia, increased appetite, and was lethargic. Three days before admission, she complained of a slight earache and was taken to a doctor. He found sugar in the urine and made a diagnosis of diabetes mellitus. At the hospital the child was stabilized on a total of 30 units of regular insulin and was discharged Jan. 19, 1939.

The disease in this girl was brought under control early; it remained mild and responded well to treatment. The child was aglycosuric at all times except during infections. This girl, in spite of efforts to change her attitude toward her disease, was ashamed to be a diabetic and was opposed to taking insulin. In the spring of 1940 she began exercising a great deal, doing housework and farm chores. She reduced her daily insulin dosage from 25 units until she was taking no insulin. Four urine specimens were examined daily. The specimens remained sugar-free except for very occasional traces. Exercise was increased if mild glycosuria occurred. She lost $3\frac{1}{2}$ pounds in weight. She did not return to school in the fall of 1940, and in November when she visited the clinic she was instructed how to decrease her diet about 200 calories so she would not require insulin during the winter when she was exercising less. During the spring and summer of 1941 she again exercised a great deal; she took no insulin and remained on the lower calorie intake per day. She lost weight.

During the first fourteen months after this adolescent girl was discharged from the hospital, when she was taking insulin and had a larger diet and less exercise, her weight increased and in relation to the average weight for her age was a plus two-thirds standard deviation.³ Her height was average for her age. Exercising and decreasing her diet and insulin reduced her weight to two-thirds standard deviation below the mean for her age during the course of the next two years.

Postinfection can be considered a critical time for diabetic patients. At this time the patient is changing from decreased activity or bed rest to normal activity. During active infection, the insulin dosage is raised to control the glycosuria due to the infection. When the infection clears up rather abruptly, the child feels better and exercises more. Unless the patient is watched closely at this time and the insulin correctly adjusted, a shock may easily be precipitated. A review of all of our well-regulated patients as to cause of shock revealed that 26 per cent of the severe shocks were postinfectious.

Prior to recognizing the importance of physical activity as a factor in diabetic management, shocks associated with increased activity were commonly encountered. The insulin dosage frequently was not decreased until the child had mild symptoms of shock. Physical activity was not routinely recorded in the home records prior to the time advice was given to make compensation for variations in physical activity. But the charts of the children observed at this earlier period showed fluctuations in insulin requirement and insulin shocks similar to those demonstrated for C. V. (Fig. 3). A review of the home records of twenty-three well-regulated patients since advice was given to compensate

for increased physical activity showed that in a total of 1,062 patient-weeks the incidence of shocks was only one reaction every six months. Eighty-three per cent were mild reactions.

DISCUSSION

Exercise is essential for good wholesome living and physical development of the young, so it should be provided for in their diabetic management. When instructing a juvenile diabetic patient in his diabetic management, an understanding of the daily routine and physical activity is necessary. A good over-all picture of the child's activity and of the factors that control or influence his activity should be obtained. A review of our diabetic progress charts for the home regulation period shows the following factors pertinent to the evaluation of exercise:

(1) Age of the child, (2) residence (rural or town), (3) distance from school, (4) physical training in school, (5) participation in sports, (6) Saturday and Sunday activity, (7) summer or vacation activity, (8) inclination to strenuous, moderate, or light muscular work or play. The study of periods of experimentally controlled physical activity at known intervals after meals and insulin administration demonstrated that such exercise is usually accompanied by decrease in blood sugar. In well-regulated children the decrease of blood sugar was small and was not accompanied by evidence of insulin shock. The study of the diabetic child or young adult in home and school situations indicates similar effects from short periods of unusual exercise; there was evidence of insulin shock from long periods of unusual exercise and from periods of increasing exercise lasting over days or weeks.

Insulin is necessary for the storage of carbohydrates. The hospital studies showed that by two and one-half hours after breakfast the normal child and the majority of the well-regulated diabetic children had normal blood sugar values and that most of the carbohydrate of the meal had been used or stored. Energy expenditure per hour varies under different conditions of muscular activity.⁴ A child weighing 100 pounds uses 43 calories per hour while sleeping, and 422 calories when walking very fast for an hour (5.3 miles).

Sometimes several disturbances are present concurrently with changes in exercise, as an infection or an emotional upset. It is impossible to estimate how much each disturbance or change affects the insulin requirement of the child. Two or more disturbances could be present concurrently for longer periods also, as, for example, the change from the emotional stress and less physical activity of school life to the relaxation and greater physical activity of vacation. One mother reported this condition was apparent at the beginning of vacation when her 13-year-old daughter, M. T., had had a conflict with her teacher and had worked under tension that year in school. The fact that some children lost weight or did not gain during the summertime indicates that exercise is probably the most important factor and not the decreased emotional strain, in lowering the insulin requirement.

In our study of exercise under home regulation, we have limited our evaluation to the well-regulated patients because these subjects generally keep better

records than those who maintain a lower level of diabetic control. It is obvious that a well-kept record is essential when the relation of exercise to diabetic regulation is being studied.

Presumably when the well-regulated diabetic child exercises more than usual, he utilizes his glucose directly for energy, and consequently he has an excess of insulin available to convert glucose into glycogen. The loss of glucose from the blood, both by utilization and storage, easily may result in hypoglycemia. If the patient has mild diabetes mellitus requiring only a small amount of exogenous insulin, his ability to compensate will be enhanced by the depression of the endogenous insulin. On the other hand if the disease is severe, requiring a large amount of exogenous insulin, the patient will have a smaller threshold of safety.

It has been observed that if the diabetes of the child is well regulated and he maintains good control, later when he becomes more mature physically and mentally he is freer from shocks of all types. The adolescent or young adult learns to judge his tolerance for exercise and his need to compensate by eating extra food for unusual periods of strenuous exercise. However, the adolescent must be advised when and how much extra food he needs, in order to prevent erratic and excessive compensation and poor dietary habits. It is preferable that extra food be eaten at mealtimes. For the young adult, the privilege of eating socially after an evening party, dance, or game has psychologic and social advantages and is provided for in our regimen.

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GRAPHS OF THE HEAD CIRCUMFERENCE OF THE NORMAL INFANT*

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THE periodic measurement of head circumference is an important item in the routine examination of the infant, and is an aid in the diagnosis of various pathologic conditions. Not only is the size of the circumference itself of interest, but knowledge of its rate of increment is of even more value. The comparison of these data, especially the rate of increment, with normal values, may be of considerable aid in the early recognition, or ruling out, of the presence of such conditions as hydrocephalus, retarded mental development, or premature closure of cranial sutures. However, due to the difficulty of interpreting the data hidden in lengthy tables now used to determine whether the increment of growth in a given case is within normal limits, this important step in the physical examination of some children is often neglected. To simplify the method of calculation, graphs were devised and are presented here for use in the clinical appraisal of the child from birth to 2 years.

In some instances the size of the head is such as to lead to a suspicion of hydrocephalus. Adequate interpretation of the data, however, may reveal simply a normal rate of growth of an unusually large head. The latter is frequently found to be a familial characteristic. On the other hand, an abnormally rapid increase in size may be demonstrated in some cases and thus confirm the suspicion of hydrocephalus earlier than would otherwise have been possible. The progress of the condition may then be followed, and in certain cases a flattening of the gradient into a normal slope may indicate the establishment of an equilibrium and a cessation of abnormal growth. Since certain types of hydrocephalus may occasionally be amenable to surgical treatment, early recognition of abnormal increase in the size of the head may permit the more prompt institution of therapy.

The knowledge that growth of the head is taking place at a subnormal rate may confirm a suspicion of mental retardation, whereas demonstration of a normal increment may go far to allay fears that a small head has similar implications. In other instances the diagnosis of premature closure of cranial sutures may be established at an early stage of the condition if cessation of normal growth is noted. Recent reports by Simmons and Peyton¹ and by Faber and Towne² have re-emphasized that early recognition is of the greatest importance, since the results of surgical treatment depend, in a large measure, upon the promptness with which this treatment is initiated. Changes in the growth pattern of the head, as compared to the normal, may indicate the seriousness of the

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*Copies of the composite graph of head circumference for males and females may be obtained from Pacific Rotoprinting Company, 306 Twelfth Street, Oakland, Calif.

condition before marked abnormality of shape, loss of vision, retardation of mental growth, or other sequelae have occurred.

During the past twenty-five years, many reports have been published giving the size of the head circumference at various ages. The data from those reports³⁻¹⁸ which contained measurements at several age periods and which were limited to normal, healthy, white children, of predominantly Northwest European ancestry, were incorporated to make graphs of head circumference for male

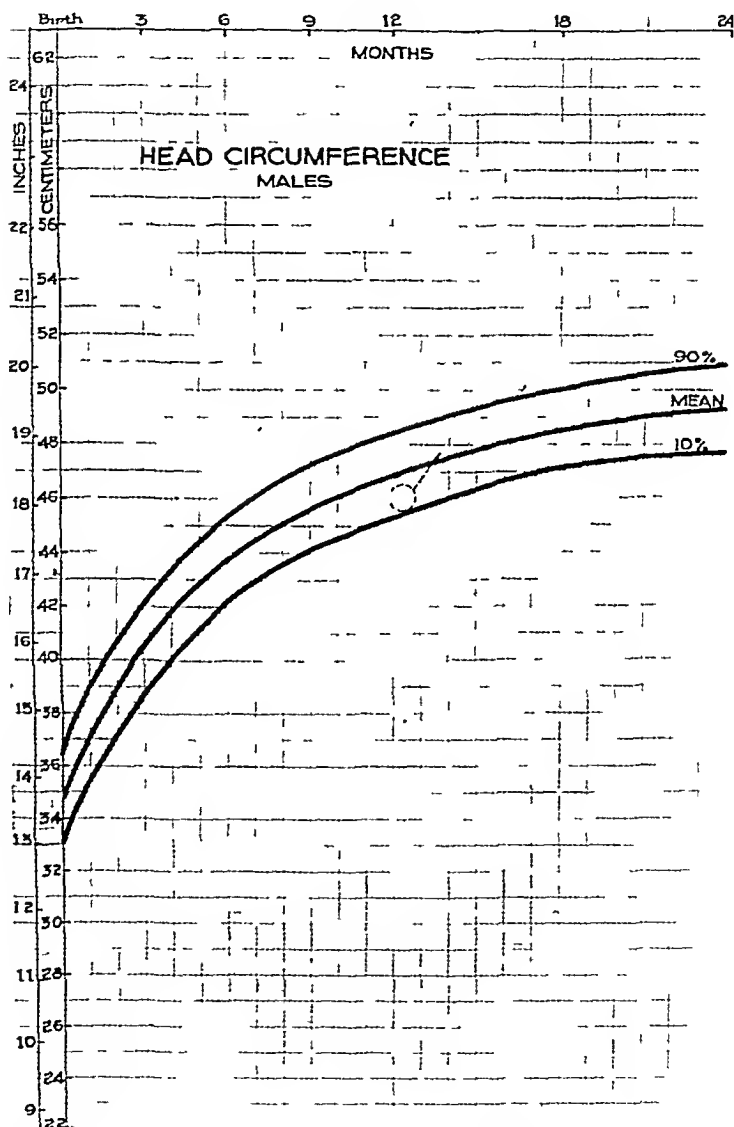


Fig 1—Graph of head circumference for male infants. (Based on data of normal healthy, white children of predominantly Northwest European ancestry.)

(Fig 1) and female infants (Fig 2) ranging in age from birth to 2 years. A composite of these two groups (Fig 3) has been found to be especially useful for reference in the office, clinic, or hospital ward.

In using the graphs it should be remembered that 20 per cent of all measurements (the largest 10 per cent and the smallest 10 per cent) will fall outside the 10 and 90 percentile lines. In this group, knowledge of the rate of increment is of particular interest since it will often reveal normal rate of growth of the head when the original measurement suggested some abnormality.

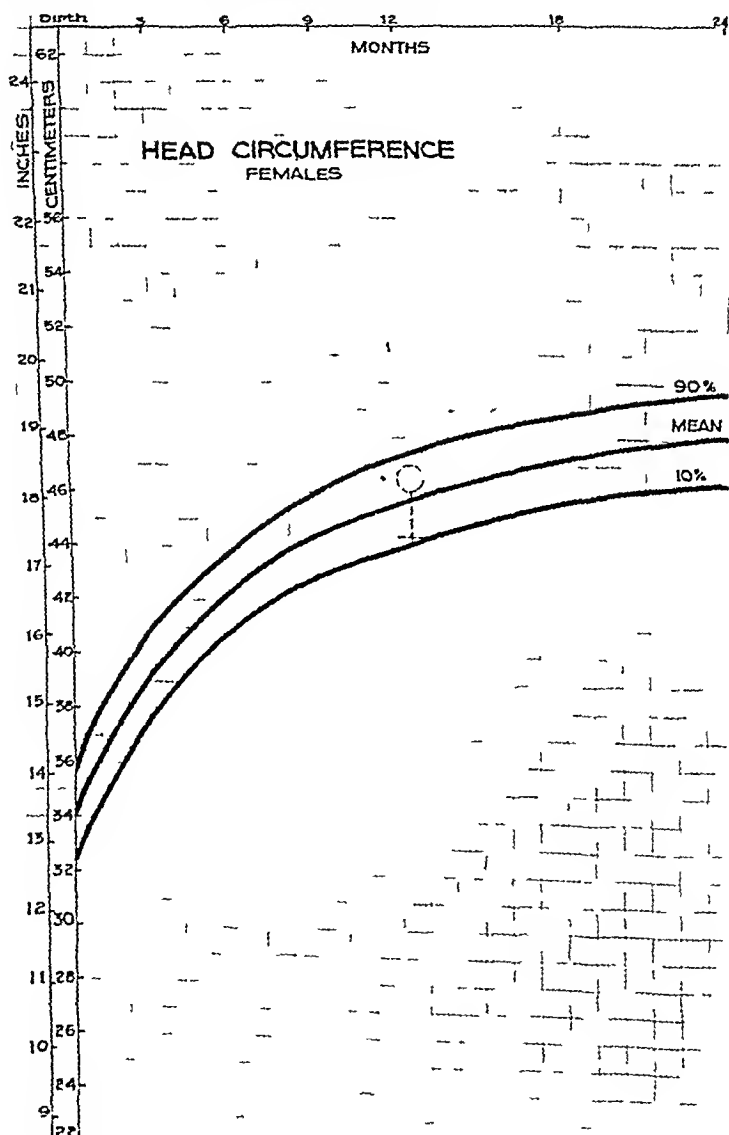


Fig. 2. Graph of head circumference for female infants (Based on data of normal, healthy, white children of predominantly Northwest European ancestry.)

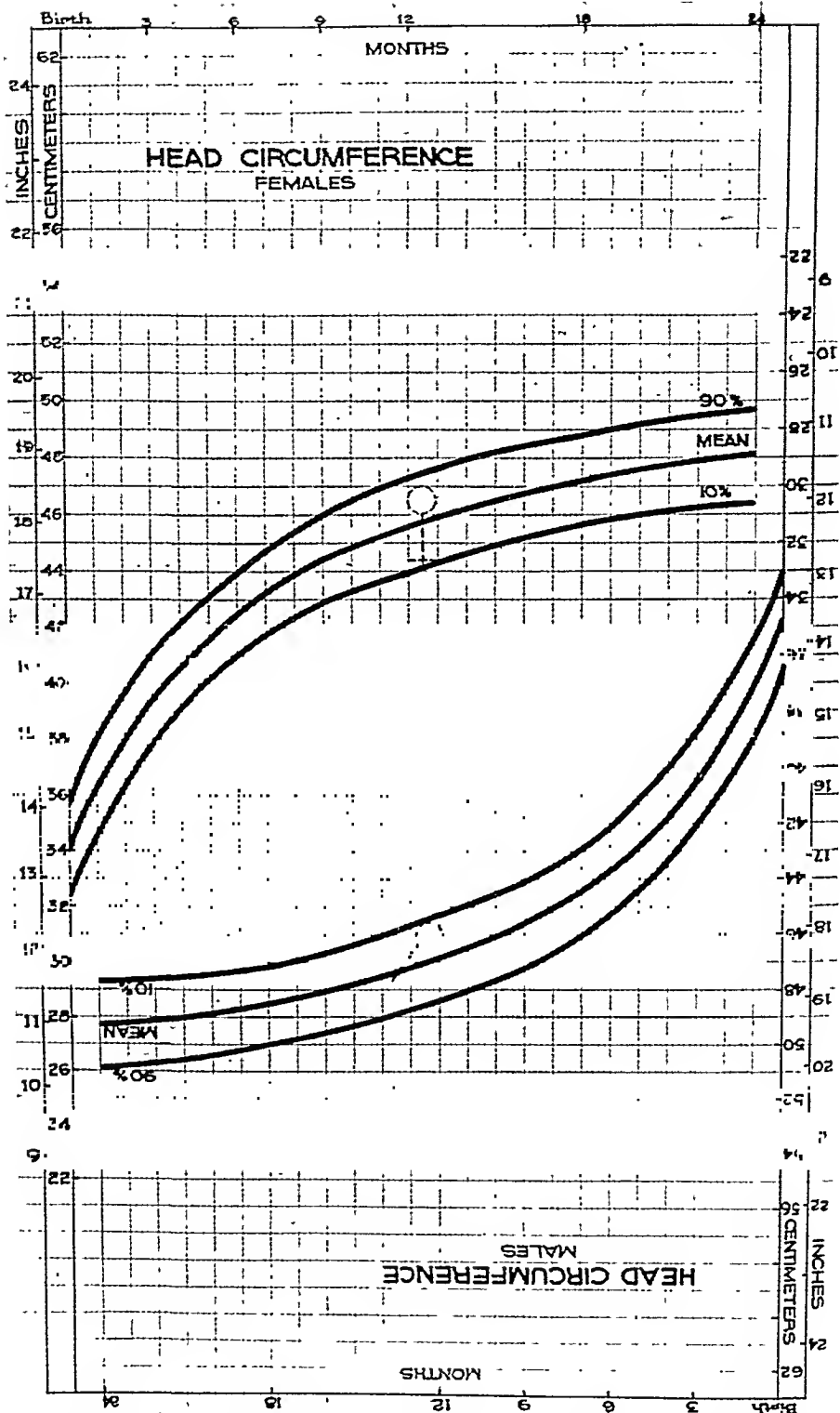


Fig. 3.—Composite graph of head circumference for *male* and *female* infants for desk use. (Based on data of normal, healthy, white children of predominantly Northwest European ancestry.)

SUMMARY

To aid in the clinical appraisal of the normal infant and in the early recognition of hydrocephalus, retarded mental development, or premature closure of the cranial sutures, graphs of the head circumference of infants are presented, which offer a convenient means of comparing with normal values both single measurements of circumference and the increment of growth of the head.

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ARTHRITIS, CONJUNCTIVITIS, AND URETHRITIS (SO-CALLED REITER'S SYNDROME) IN A FOUR-YEAR-OLD BOY

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IN 1916, during World War I, Reiter¹ described a patient in the German army who developed arthritis, conjunctivitis, and urethritis following an episode of diarrhea. Since then a number of other instances, almost all in adult males, have been reported. Most of these have been recently reviewed by Vallee.² The syndrome usually begins with either urethritis or purulent conjunctivitis. Dysuria and frequency of urination are associated with the urethritis. The conjunctivitis is occasionally followed by keratitis, iritis, and iridocyclitis. Later the joints, particularly those of the ankle and knee, become acutely inflamed and tender. This arthritis is often migratory, but may be limited to a single joint. Hydroarthrosis is common, but destructive changes in the joints are infrequent. There is usually a low-grade fever, a moderate elevation of the leucocyte count, and an increase in sedimentation rate. The clinical course is often characterized by remissions and exacerbations but usually terminates favorably in two to four months. Although it was in 1942 that the first account of this syndrome appeared in the American literature,³ many patients among our troops during World War II were recognized as presenting this triad of symptoms.⁴⁻⁶

To some observers, Reiter's syndrome is not an etiological entity (see references of Young and McEwen⁶); however, to most others there appears to be a relationship to some definite infection. Although a spirochete was demonstrated in the blood of Reiter's patient,¹ most observers have tended to disregard this finding. In recent years attention has centered about an association with dysentery bacteria,⁶ pleuropneumonia organisms,² or some as yet not clearly defined viruses.^{7, 8}

It is the purpose of the present communication to give the case history and results of the bacteriologic, virologic, and immunologic investigations in a 4-year-old boy who became ill and developed the classical Reiter's syndrome. It is believed that this is the first recorded instance of this disease in a child.

CASE REPORT

R. K., a 4-year-old white male child, was admitted to The Mount Sinai Hospital Pediatric Service on Aug. 16, 1947, because of inflamed eyes, a swollen painful right knee, and painful urination of two days' duration.

Family History.—Both parents had seasonal hay fever. A sibling, 10 months old, was living and well. The family history was otherwise noncontributory.

Past History.—The child's birth, early growth, and development were normal. Except for frequent upper respiratory infections and an uncomplicated attack of measles he had been well. One month prior to admission, during a routine physical examination, a cardiac murmur was noted. There was no antecedent history of rheumatic or cardiac symptoms.

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Present Illness.—One week prior to admission the patient had watery diarrhea. However, the stools did not contain blood, mucus, or pus, and were normal after three days. For two days preceding admission, there were urgency, frequency of urination, and dysuria. At the same time both eyes were observed to be inflamed. On the morning of admission the child appeared feverish, and his right knee was swollen and painful. He refused to walk or stand. There were no complaints referable to any other joints. Although the mother had had diarrhea at about the same time as the child, neither she nor the other members of the family showed symptoms similar to those presented by the patient.

Physical Examination.—The child appeared to be acutely ill and moderately febrile. He was normally developed, but somewhat pale and underweight. The rectal temperature was 102° F., the pulse was 96, respirations 20, blood pressure 98/60 (R.A.). His weight was 31.4 pounds (14.2 kg.). There was a bilateral purulent conjunctivitis with acute inflammation and edema of both palpebral and bulbar conjunctivae and marked chemosis. Moderate photophobia and blepharospasm as well as increased lacrimation were noted. The remainder of the eye examination including funduscopy was not remarkable. Small preauricular nodes were palpable bilaterally. The results of examination of both ears and nose were normal. There were no mouth lesions. The tonsils were hypertrophied and slightly injected. The neck was supple, and the trachea was in the midline. There was a mild generalized lymphadenopathy. The heart was not enlarged on percussion; the rhythm was regular and the rate was not rapid. There were no thrills or shocks. The heart sounds were of good quality. At the apex and along the left sternal border extending to the pulmonary area a blowing, soft systolic murmur was heard. This was not transmitted to the axilla, and was not audible over the neck vessels, back, or to the right of the sternum. The second pulmonary sound was louder than the second aortic sound, but was not accentuated. The pulses were equal, synchronous, regular, and of good quality. The lungs were clear to percussion and auscultation. The abdomen was scaphoid, there was no tenderness nor spasm. The liver, spleen, and kidneys were not palpable. Examination of the extremities was normal except for the right knee, which was swollen, warm, and held in a position of slight flexion. There was spontaneous pain and moderately severe tenderness on palpation. Motion was painful and resisted. There was moderate effusion into the joint, so that a patellar click was readily demonstrable. The genitalia were those of a normal 4 year old boy, but the urethral os was slightly everted. The neurological examination was not remarkable. The skin was slightly pallid, but no unusual lesions were noted.

Course.—The patient's temperature, which shortly after admission rose to 103° F., gradually fell to normal by the end of the third week (Fig. 1).

Warm, wet saline compresses were applied to the right knee, which was elevated on pillows. On the third hospital day the knee joint was aspirated for diagnostic purposes. Approximately 10 ml. of thick, turbid, odorless, yellow green pus were withdrawn, and 100,000 units of penicillin in 5 ml. of normal saline were injected directly into the joint cavity. The pus, which contained 17,000 leucocytes per cubic millimeter, all polymorphonuclear, was studied for possible bacterial and viral content. From the third hospital day the patient ceased to complain of spontaneous pain in the right knee, although tenderness on pressure persisted. On the sixth hospital day, at the advice of an orthopedic consultant, 4 pounds of traction were applied to the right lower extremity by means of a Buck extension to correct a tendency toward flexion contracture of the knee. As shown in Fig. 1, the subsequent course of the arthritis was one of progressive improvement, so that at the time of discharge, forty four days after the onset of arthritis, only minimal residual effusion remained with no evidence of deformity or limitation of motion. One month later minimal effusion was still apparent, but two months after discharge, the right knee was entirely normal on clinical examination. Several x-ray studies failed to reveal more than soft tissue swelling with increase in the joint space; no bony abnormalities were found.

The dysuria, frequency, and pyuria subsided at the end of the first week of hospitalization. On the third hospital day some urethral pus and a small amount of prostatic fluid were obtained for study for possible bacterial or viral content.

There was slow but progressive improvement in the condition of the eyes until the eighth hospital day, when an exacerbation of the bilateral purulent conjunctivitis was observed (see Fig 1). On the following day, the temperature rose to 101° F, and the conjunctival reaction was more marked. In addition, there was noted for the first time some corneal involvement of the right eye. The child was then treated with sulfathiazole ophthalmic ointment, drops of 1 per cent atropine sulfate, warm saline compresses, and injections of boiled milk. After the second week of hospitalization, definite improvement was again noted. The conjunctival reaction diminished, the corneal infiltrates were smaller, and the blepharospasm and photophobia were less apparent. At the time of discharge, thirty three days after the onset of keratitis, the only residual defect was a small, faint, peripheral opacity of the right cornea, the left cornea had cleared entirely.

At no time during the patient's course in the hospital or during the subsequent months of observation did he exhibit recurrence of the diarrhea noted at the onset of the illness.

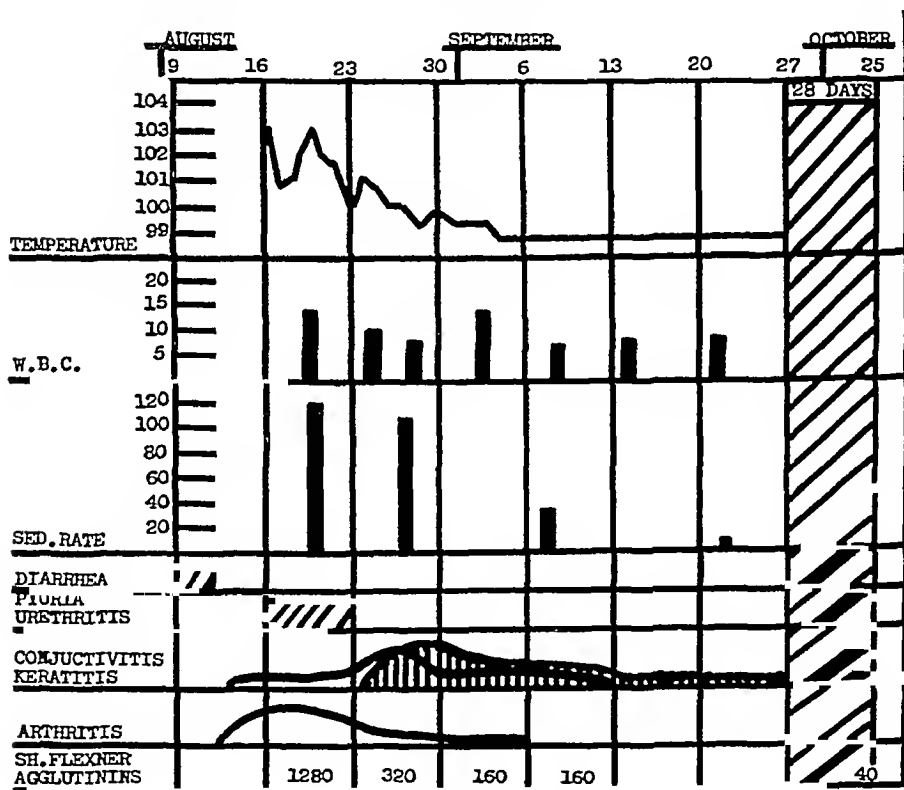


Fig 1—Summary of clinical course of patient

Upon admission, the hemoglobin was 12 Gm, and there was a white blood cell count of 20,050 per cubic millimeter with 79 per cent polymorphonuclear cells. Subsequent blood counts were essentially normal as is graphically recorded in Fig 1. The sedimentation rate was 120 mm per hour (Westergren) on admission. It remained quite rapid during the first three weeks in the hospital and did not reach normal levels until the sixth week.

Tuberculin reactions (Mantoux) were negative up to one milligram. The Schick test was negative. Blood urea nitrogen, total protein, and albumin globulin partition were within normal limits. Repeated tests were made for the development of agglutinins to enteric and other bacteria and are reported below.

During the first ten days of hospitalization the patient was given a course of penicillin therapy in divided doses of aqueous solution every three hours intramuscularly, and penicillin

ophthalmic ointment locally. It is noteworthy that the onset of keratitis occurred during this period of therapy. Subsequently, the already described eye care was given, and sulfadiazine was also given by mouth in dosage of 0.12 Gm. per kilogram of body weight daily for nine days. Despite the progressive clinical improvement noted during this period, it cannot be stated that sulfadiazine exerted any influence on the course of the disease.

Six weeks following discharge the child was readmitted because of a mild conjunctivitis associated with an upper respiratory infection. He was afebrile, and the white blood count and sedimentation rates were normal. There were no urinary symptoms nor urethral discharge. The urine was clear. Conjunctival smear and culture were also negative. There was no diarrhea. Stool culture revealed no pathogen. The joints including the right knee were normal.

When seen four months after the onset of the illness, the only residual abnormality was a minute peripheral opacity of the right cornea, which did not interfere with the child's vision.

BACTERIOLOGY

Material from the conjunctivae and from the affected knee joint obtained shortly after admission was inoculated onto blood agar and chocolate agar plates and into 20 per cent serum broth tubes, which were incubated aerobically and under increased carbon dioxide tension for two weeks. The only organisms recovered were a *Staphylococcus albus* from the conjunctivae and a chromogenic bacillus from the knee fluid. Neither was thought to be significant. Smears of prostatic fluid were stained by Gram's technique, but no organism could be demonstrated. Despite the history of recent diarrhea, only *Escherichia coli communis* was recovered from stool cultures taken the day after admission in tetrathionate broth and on S S, Endo, blood, and nutrient agar plates. Blood cultures also taken on admission in meat extract, glucose, and nutrient broth flasks and liver tubes were negative after two weeks of observation.

VIROLOGY

Rabbit corneas were scarified and inoculated with some of the urethral discharge and knee fluid. The specimens were obtained on Aug. 18, 1947, and stored in Lusteroid tubes at approximately 20° C. until satisfactory animals became available. On Sept. 4, 1947, two full-grown rabbits were inoculated with each specimen, and on Sept. 11, 1947, this experiment was repeated using young rabbits, each weighing approximately one kilogram. Although these animals were observed daily for two weeks, no abnormalities were noted. A group of five Swiss mice were also given 0.03 ml. intracerebrally and 0.1 ml. intraperitoneally of the fluid obtained from the patient's knee. They, too, failed to develop any abnormalities during a two-week observation period.

IMMUNOLOGY

Coccoccus complement fixation tests, using the Lederle antigen, were negative with sera obtained Aug. 18 and Sept. 15, 1947. Agglutination tests with serial specimens of serum collected during a three-month period against a pleuropneumonia-like organism which had been recovered from a patient with subacute bacterial endocarditis² were carried out for us by Herschberger. These results were also negative. Similarly, agglutination tests were negative for the

development of antibodies for *Eberthella typhi*, *Salmonella*, *Brucella*, and *Proteus OX-19* bacteria. However, antibodies in high titer were found for *Shigella flexner VII* and *VIII*. No similar levels were detected for the other Flexner strains. As is indicated in Fig. 1, the results of the child's agglutination tests for *S. flexner VII* fell from a level of 1:1,280 shortly after admission to 1:40 several weeks later. Although this trend was true in many repeated tests, the charted results were obtained with an antigen prepared from an overnight culture on nutrient agar, which was washed three times and killed with 0.5 per cent formalin. From a heavy "stock" suspension, an antigen approximately the turbidity of a MacFarlane No. 3 standard was prepared immediately before use. Serial dilutions of serum were made in 0.4 c.c. quantities of saline. To each an equal quantity of antigen was added. The tubes were shaken, incubated in a 56° C. water bath for one hour, and left at 4° C. overnight before reading. All readings were made by one of us with the aid of a magnifying glass. The highest dilution yielding a 2-plus agglutination (plus 4 = complete agglutination; 0 = no agglutination) was considered the end point.

DISCUSSION

The clinical picture presented by this child was that of an infection.

Although it is well known that the triad of arthritis, conjunctivitis, and urethritis can be produced by the gonococcus, it was felt that gonorrhea was excluded in this instance both by culture and by serologic tests.

The failure to recover a virus from this patient does not exclude the possibility that a virus was the etiological agent of the illness. The storage of specimens before inoculation of the rabbits and mice was not ideal. However, according to Buddingh,¹⁰ the virus recovered by him on the rabbit cornea from a patient with Reiter's syndrome would have survived this storage. Because that virus is said to cross immunologically with the one recovered by Buddingh and Dodd¹¹ from newborn infants with epidemic diarrhea, it is unfortunate that it has not yet been possible to test our patient's serum for neutralizing antibodies against either of these agents.

No pleuropneumonia organisms were recovered. However, search was limited to culture of urethral discharge and knee fluid in serum broth and on chocolate agar. The negative results of the agglutination test with the pleuropneumonia organism of Hersehberger and her associates⁹ are also of limited significance inasmuch as the degree of immunologic crossing among the various pleuropneumonia strains is not yet known.

The high titer of *S. flexner VII* agglutinins observed in this child's blood ten days after onset of the diarrhea and the subsequent progressive decline would suggest that the diarrhea had been caused by this or a related shigella, despite the recent work by Watt and DeCapito,¹² which shows the unreliability in adults of the agglutination test in such infections. Failure to recover this organism from the stool approximately one week after cessation of diarrhea is not unusual.

It is of considerable interest that in the original as well as in a great many of the other reported cases of this syndrome there was a preceding history of

diarrhea This fact has been recently emphasized by Young and McEwen.⁶ It is also known that arthritis may be a complication of bacillary dysentery and that it frequently appears after the acute symptoms have subsided The fluid from the joints in such arthritis is usually sterile¹³ Conjunctivitis and iridocyclitis are also recognized complications of dysentery infections¹⁴

Study of a single case does not permit an answer to the question of whether this syndrome represents a specific entity or is a nonspecific response of certain individuals to a variety of infections—perhaps an “allergic” response However, the fact that Reiter’s triad of symptoms occurred in a 4-year-old child is significant, especially since the syndrome would seem to be very uncommon in this age group, one in which diarrhea is not infrequent

SUMMARY

The case history is presented of a 4-year-old boy who, following a short period of diarrhea, developed arthritis, conjunctivitis, and urethritis Recovery from this syndrome, which was originally described by Reiter, was accompanied by a gradual decline in *S flexner* agglutinins from a level of 1:1,280 to 1:40 The significance of this observation is not clear Attempts to recover a pathogenic microorganism, pleuropneumonia-like organism, or a virus from the joint fluids, urethral discharge, and conjunctival smears were unsuccessful

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PARA-AMINOBENZOIC ACID BLOOD LEVELS

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THE clinical value of para-aminobenzoic acid in the treatment of rickettsial diseases has been well established, not only in adults, but also in children. It is our purpose to present the results of a study on the absorption and urinary excretion of para-aminobenzoic acid administered orally, subcutaneously, and intravenously. It is not our aim to formulate a dosage schedule, but only to show the blood levels which may be obtained with different dosages.

METHODS

Our observations were made upon infants and children on the pediatric ward. No adult subjects were used. None of the patients had a rickettsial disease. The subjects were not restricted in any way during the study, being allowed to consume *ad libitum* and to take their meals.

All blood samples were collected in test tubes containing sodium citrate crystals so that no dilution would occur. Para-aminobenzoic acid levels were determined on whole venous blood by a modified Bratton-Marshall method as described by Kireh and Bergeim¹ and Eckert.² The free form of para-aminobenzoic acid was always determined, and the conjugated form when it was felt that this would add to our study. All blood level determinations were performed by the same person (L. A.).

OBSERVATIONS

Para-aminobenzoic acid was administered orally as the sodium salt in the form of tablets (0.25 Gm. and 0.5 Gm.) and, in three cases, as a suspension containing 5.0 Gm. in 30.0 c.c. At no time was para-aminobenzoic acid given by gavage. When a single oral dose (0.1 Gm. per kilogram of body weight) was given, the blood level rose rapidly, in most cases reaching its maximum in the first two hours, and then gradually fell, until only a trace remained at the end of six hours (Fig. 1). The variance in the values and in the rapidity of attaining the maximum levels cannot be explained by differences in the size of the subjects, as their weights ranged from 20 to 25 kg. We are not able to comment upon the ability of the gastrointestinal tract to absorb para-aminobenzoic acid, as no fecal excretion studies were performed. One might surmise, however, from the high percentage excreted in the urine (Fig. 11) that the absorption is fairly complete. When oral doses of 0.2 Gm. per kilogram of body weight were given, the maximum blood levels, as would be expected, were higher (one and one-half times) and more prolonged than with the smaller doses. At

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the end of the six-hour period the levels were some twenty-five to 100 times as great (Fig. 2). The rapidity of the fall of the blood levels in all of these studies was influenced by the liquid intake of the individual, as this was not restricted.

Fig. 1.

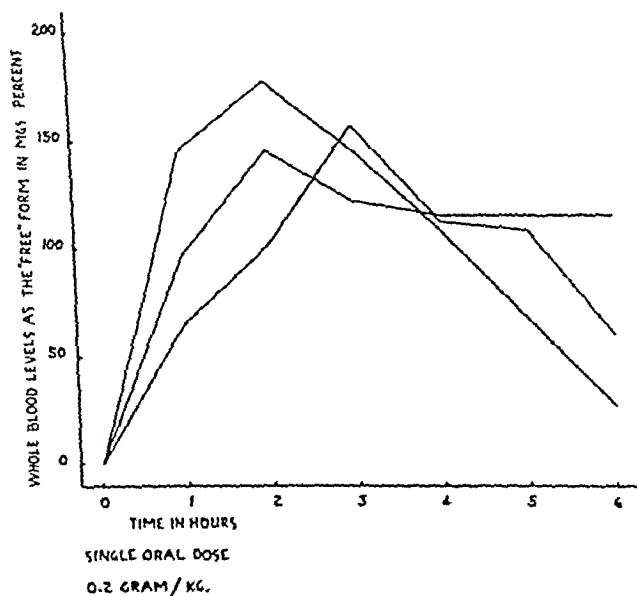
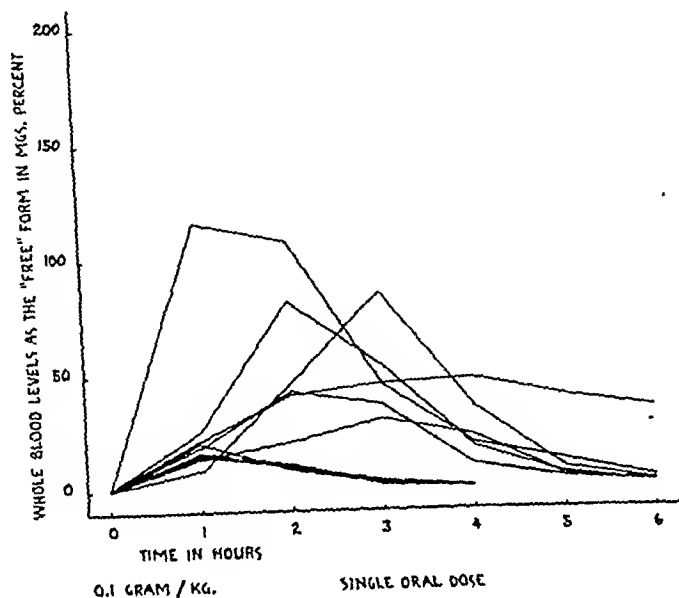


Fig. 2

Our studies on multiple oral doses are summarized in Figs. 3 and 4. It is apparent that 0.025 Gm. per kilogram of body weight at three-hour intervals does not maintain significant levels. Twice this amount, however, maintained

Fig. 3.

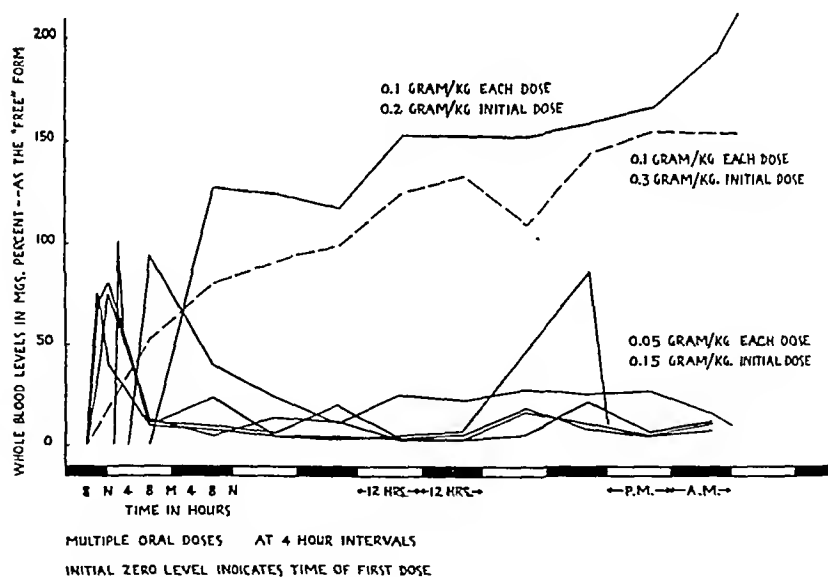
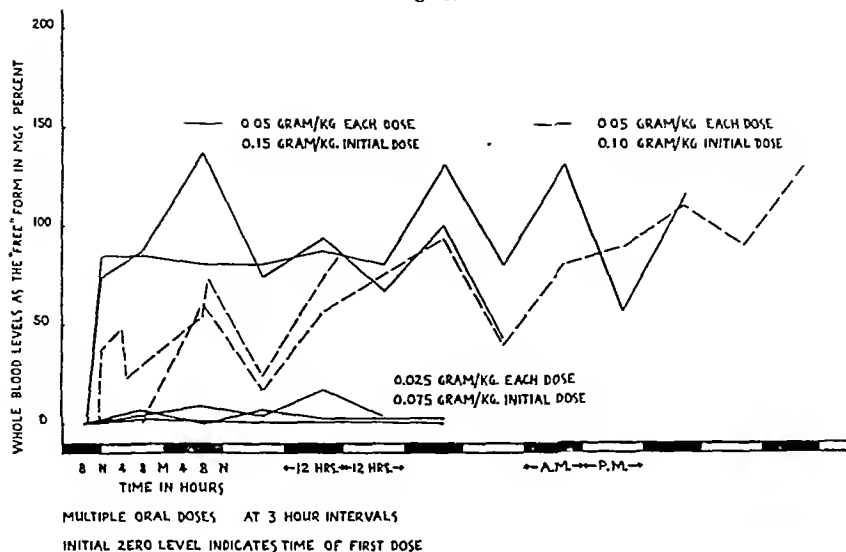


Fig. 4.

Fig. 5

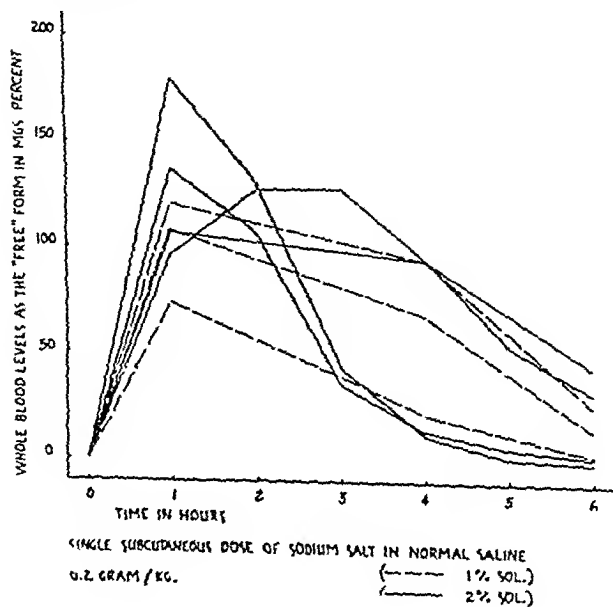
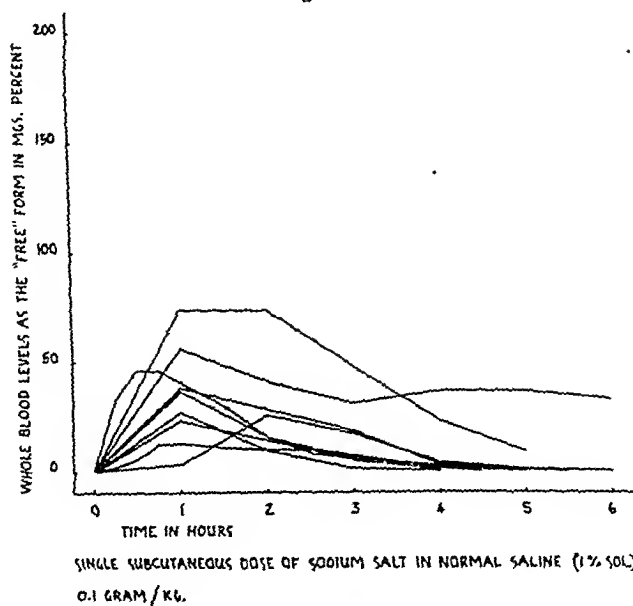


Fig. 6

levels averaging 75 to 100 mg. per cent. This same amount (0.05 Gm. per kilogram) at four-hour intervals did not maintain significant levels. At this same time interval (four-hour) 0.1 Gm. per kilogram of body weight produced ex-

Fig. 7.

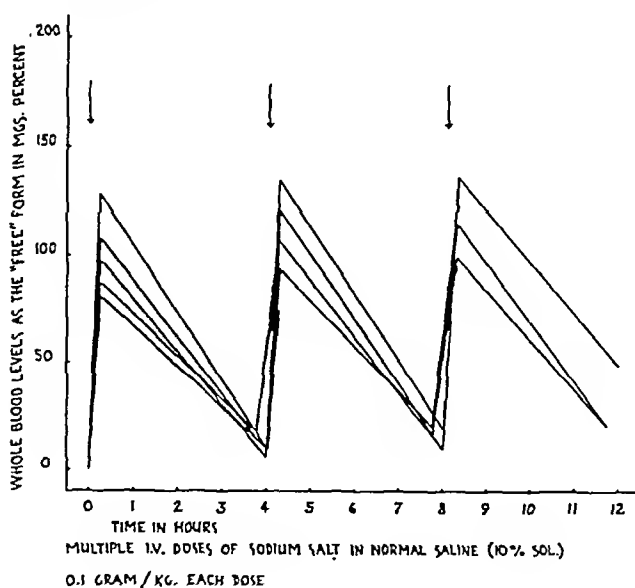
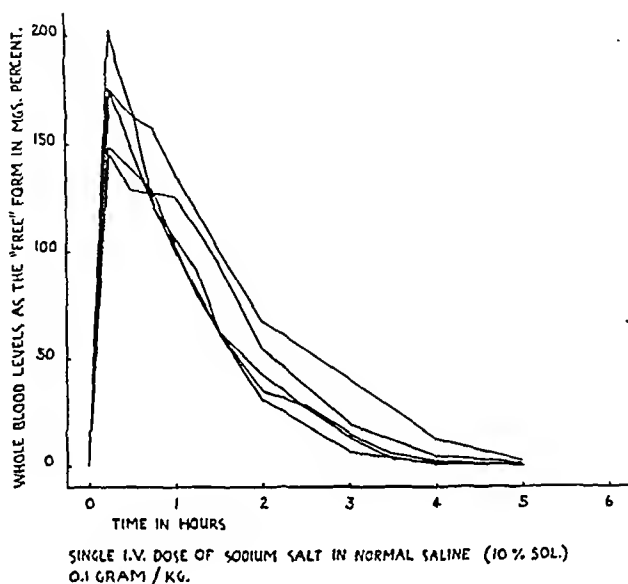


Fig. 8.

ceedingly high levels. It is of interest that these figures show that the early morning levels were always higher than at other times of the day; this was probably due to voluntary restriction of liquids during the sleeping hours.

Para-aminobenzoic acid in the form of its sodium salt may be administered parenterally. The need for parenteral therapy has been emphasized by Ravenel.³ The drug may be administered either subcutaneously or intravenously. The maximum levels obtained by subcutaneous injection (0.1 Gm. per kilogram of body weight as a one per cent solution in normal saline) were not as great as when the drug was given orally, but were attained more rapidly (Fig. 5). The blood levels were increased when the dose was doubled (0.2 Gm. per kilogram of body weight) (Fig. 6). Moreover, when this same dose was given in a 2 per cent solution, the blood levels were further increased. There were no reactions when this drug was administered subcutaneously in solutions as strong as 3 per cent in normal saline.

An immediate blood level rise to over 150 mg. per cent was obtained after giving sodium para-aminobenzoic acid intravenously (0.1 Gm. per kilogram of body weight as a 10 per cent solution in normal saline). Following this, the level rapidly declined (Fig. 7). Multiple intravenous injections given at four-hour intervals failed to produce a sustained blood level (Fig. 8).

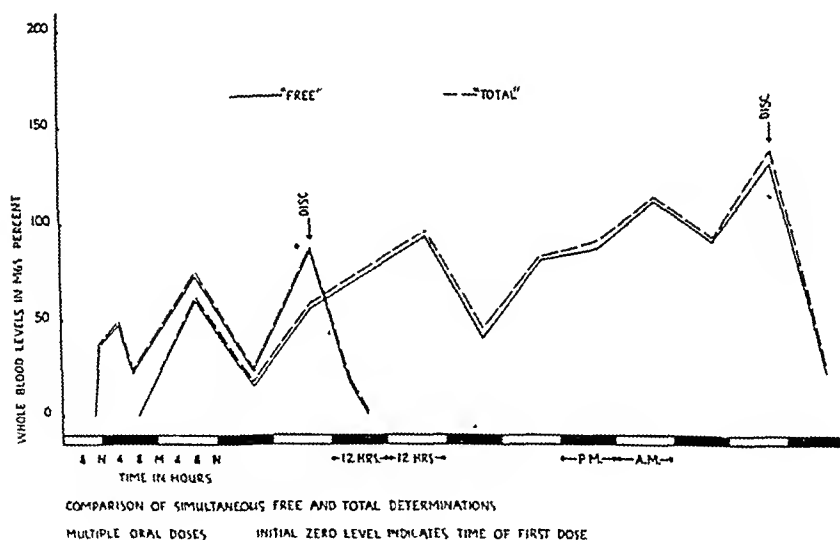


Fig. 9.

Values for total para-aminobenzoic acid were slightly higher than for the free form. The two values paralleled each other throughout (Fig. 9). The difference between the levels is accounted for by the conjugation (acetylation) of a small portion of the drug within the body. It is worthy of note that the percentage of the conjugated form did not increase when the drug was given over a period of several days.

It will be noted that following administration of a single dose by any route used in this study, the drug has largely disappeared from the blood in about six hours. The rapidity of the disappearance seems to be inversely related to the height of the blood level obtained. When the drug was discontinued fol-

Fig. 10.

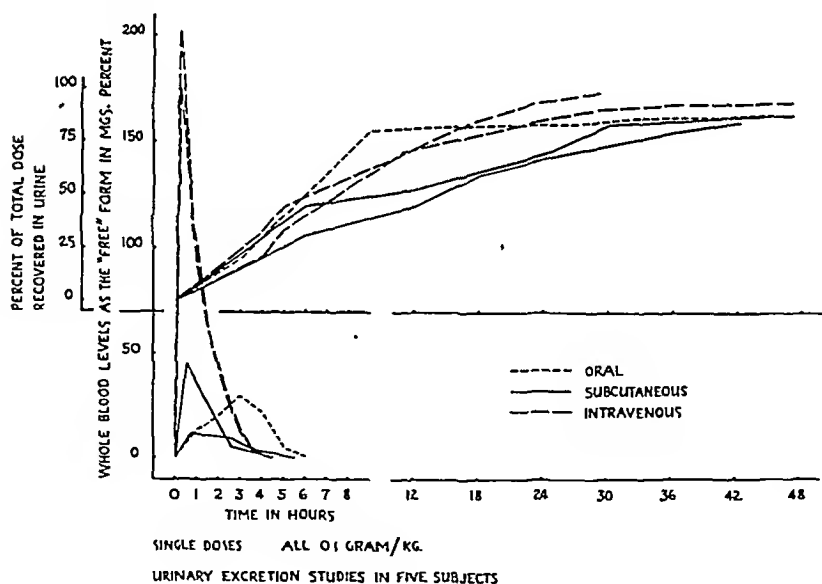
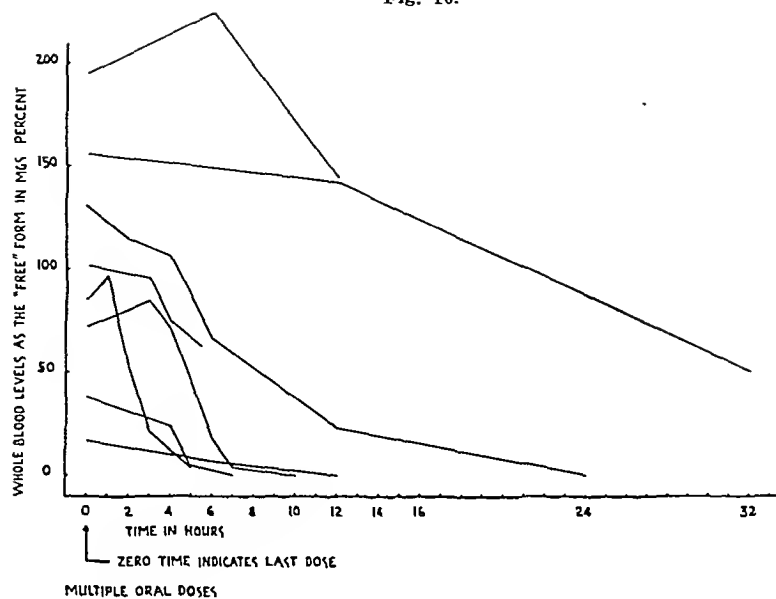


Fig. 11.

lowing multiple oral doses (Fig. 10), it possibly persisted in the blood for a somewhat longer period of time. These results may be suggestive of storage of para-aminobenzoic acid within the body for at least a short period of time. Moreover, the results shown in Fig. 11 demonstrate that, following a single dose, urinary excretion is continued for more than twenty-four hours after the drug has disappeared from the blood.

Each subject receiving para-aminobenzoic acid was followed with hemograms and urinalyses. No abnormalities were noted. Vomiting was minimal.

CONCLUSIONS

Para-aminobenzoic acid is rapidly absorbed from the gastrointestinal tract. An adequate blood level is maintained in most instances when one-half or one-third the initial dose is given as a maintenance dose every three hours. Subcutaneous administration of solutions as strong as 3 per cent were without ill effects. The rapidly rising blood levels and the maintenance of these levels over a period longer than six hours makes this method of administration feasible and useful. Intravenous administration of the drug produced high levels rapidly, but these were not maintained. The prolonged excretion of the drug in the urine is suggestive of storage within the body.

We wish to express our appreciation to Dr. Edwin E. Garrett for his aid in this study.

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INCIDENCE OF SICKLE CELL ANEMIA WITH RHEUMATIC HEART DISEASE

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THE confusing resemblance between the symptoms of sickle cell anemia and those of rheumatic heart disease is well known. Yater and Hansmann¹ have pointed out that the diagnosis of rheumatic heart disease in cases of sickle cell anemia has been made many times from the history of joint pains, presence of an enlarged heart, systolic mitral or precordial murmur, and hepatomegaly. Other common symptoms are leg pain, ankle edema, pallor, and dyspnea. Often-times organic heart disease is diagnosed clinically only to find at autopsy that all changes noted are compatible with a severe anemia.

That anemia is a cause of heart disease has often been overlooked. In accordance with the Criteria Committee of the New York Heart Association, the criteria are as follows: (1) presence of a marked anemia, (2) disturbance of cardiac function, (3) disappearance of signs and symptoms after relief of the anemia.

Sickle cell anemia is hereditary and is somewhat refractory to treatment. It is characterized by exacerbations and remissions, and therefore the third criterion cannot be satisfactorily met except for relatively short periods of time. Over a period of years, the anoxia secondary to the anemia gives rise to alternating severe strains upon the heart. This relationship of cause and effect between the anemia and cardiac abnormalities cannot be overlooked nor can it be denied.

In 1932 Anderson and Ware² reviewed the literature and found cardiac enlargements in 76 per cent and murmurs in 87 per cent of those cases in which mention was made of the presence or absence of these findings. Klinefelter³ has shown that the clinical findings in sickle cell anemia could closely simulate those of rheumatic heart disease, but noted that specific lesions have never been demonstrated at autopsy. Hansman emphasized the importance of being extremely cautious in making a nonanemia diagnosis of heart disease when studying a patient with sickle cell anemia. The clinical discussion as to whether sickle cell anemia alone is present or whether there is an accompanying rheumatic heart lesion is made even more complex by Cooley's⁴ statement: "Organic heart disease is about as common here (sickle cell anemia) as in any group of children subject to tonsillitis as these children often are."

In an attempt to clarify the confusion, the pathology files of the Cook County Hospital were searched in order to ascertain the incidence of sickle cell anemia concomitant with rheumatic heart disease. Since 1929, fifty-three autopsies have been performed on individuals who gave positive evidence of sickle cell anemia. In thirteen cases, or 24 per cent, the sickle cell anemia was

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the direct cause of death. Of this group, ten patients were below 3 years of age. In forty cases, or 76 per cent, the sickle cell anemia contributed indirectly to the cause of death. Of this group, four patients were below 3 years of age. Three patients showed evidence of rheumatic heart disease, and the primary anatomic diagnosis in two of these was rheumatic heart disease. The ages of these three patients were 3, 7, and 22 years. The incidence of sickle cell anemia concomitant with rheumatic heart disease was 5.6 per cent.

CASE REPORTS

CASE 1.—Negro girl, aged 22. Several months prior to the present admission the patient had been in this hospital. At that time she gave a typical history of rheumatic heart disease with cardiac involvement since childhood; her complaints were severe dyspnea, orthopnea, constant precordial pain, and some peripheral edema. It was also found that she had an active case of sickle cell anemia. She remained in the hospital for eight weeks and was discharged. At the time of the second admission, which was twelve weeks after her previous discharge, her complaints again were precordial pain, weakness, nodules in the calves, cough, and slight hemoptysis.

Physical Examination.—The temperature was 99.6° F., pulse 112, respirations 24, blood pressure 90/50. There was marked pallor of the conjunctivae, the heart was enlarged to the left with a loud systolic and presystolic murmur; the rhythm was regular, the tones distant, P₂ accentuated. The liver was felt below the level of the umbilicus. There was slightly diminished resonance in the lower lobe of the right lung.

Laboratory Findings.—On x-ray the heart showed a mitral configuration. The hemoglobin was 9.5 Gm., the red blood count 3.65 million, the white blood count 10,150. There was marked sickling. The urine was negative except for 3 plus albumin on one occasion.

Further Course.—The patient remained in the hospital until her death six weeks after admission. During her hospital stay she was given repeated blood transfusions and put on a regular cardiac regimen. There was, however, no relief of her symptoms, and she gradually became worse and died.

Autopsy Report.—The body was that of a well-developed, well-nourished Negro girl, who showed no external pathologic findings; there was no edema of the ankles.

Heart: The heart weighed 550 Gm. The wall of the left ventricle measured 18 mm. in thickness and that of the right ventricle, 5 mm. The myocardium was pale purple-red; there were numerous fibrous tags attached to the epicardium with many pinhead-size subepicardial hemorrhages. The free edge of the mitral valve revealed many pinhead-size single and confluent light yellow-gray, soft elevated nodules. These were also present in the endocardium along the left auricle near the mitral valve. All chambers were dilated markedly and the endocardium of both auricles and of the interventricular septum was gray-white and thickened. The papillary muscles were hypertrophied. There were numerous fibrous adhesions of the pericardial sac to the epicardium. Both coronary arteries were thickened markedly; there were many atheromatous plaques, but the lumen was patent throughout. The pulmonic valve measured 76 mm. There was a single fatty and hyaline plaque.

Spleen: The spleen weighed 140 Gm. It was very firm, and the capsule was slightly thickened and smooth. On section, dark purple-red trabeculae were prominent. The lower pole was located at the ninth rib in the midaxillary line.

Liver: The liver extended 12 cm. below the xiphoid process and 3 cm. below the costal margin. It weighed 2,000 Gm., was very soft and flabby, and the capsule was thickened. There were many adhesions attached to the capsule of the right lobe. On section, deep red-purple and acinar centers were confluent, leaving small islands of light yellow peripheral acinar markings.

Bone marrow: The bone marrow was cherry red.

Microscopic examination.—

Heart: The muscle fibers were swollen and hypertrophied; the nuclei were oval to barrel-shape; the cytoplasm was pale pink and granular. Cross-striations were indistinct. There was

an increase of interstitial fibrous connective tissue, more marked around the large vessels. The epicardium was edematous and thickened with round cell infiltration. The capillaries were dilated. The fat stain showed slight deposition of fat in muscle fibers.

Liver. The architecture was destroyed. There were remnants of liver cell cords around the portal triad and near the capsule, which were swollen, purplish pink, and had granular cytoplasm. Sinusoids of these cells were moderately compressed and contained red blood cells, and a few round cells. Kupffer cells were prominent and numerous. The remainder of the liver cell cords were intact and showed normal liver cells. There was a deposit of hemosiderin pigment granules in the macrophages throughout the entire section. The portal triad showed slight proliferation of bile ducts. Sudan III stain revealed a deposition of sudanophilic droplets in the remaining cords. The red blood cells were thin and sickle shaped.

Spleen. The capsule was of normal thickness. The sinusoids were enormously congested with red blood cells which were thin and sickle shaped. There were many polymorphonuclear leucocytes scattered throughout. The lymphoid tissue was sparse and most of it was around the central arteries. Here and there were hyalinized, light pink areas, which appeared to contain free hemoglobin. There were many hemosiderin pigment granules throughout.

Bone marrow. There were more centers of erythropoietic activity than normally found. The granulocytic elements were of ordinary distribution. The megakaryocytes were numerous throughout.

CASE 2—Negro boy, aged 7. The patient was well until three days prior to admission when he developed abdominal pain. This lasted one hour, and then he developed pain in the left groin and leg. This was transient, the pain was next felt in the head and shoulders, only to return to the stomach two days later, when he vomited once. There was nocturia with the voiding of reddish urine one to three times each night. His past history revealed that he had had several attacks of typical rheumatic fever, beginning at one year of age, and swelling of the feet at 4 years of age.

Physical Examination.—The patient was undernourished. There were markedly hypertrophied postauricular nodes, mild axillary lymphadenopathy, markedly enlarged bilateral inguinal nodes, and slightly tender epitrochlear and posterior popliteal lymph nodes. The lungs were negative. The pulse was 140 per minute. There were blowing systolic and diastolic murmurs. The liver was felt one fingerbreadth below the costal margin and was slightly tender. The temperature was 102° F. The patient had long tapering fingers.

Laboratory Findings.—On x-ray, the heart was enlarged in its transverse diameter and had a contour of mitral type. The hilar and perivascular markings were increased, suggesting some passive congestion.

The red blood count was 2.14 million, the white blood count 25,000, with 69 per cent polymorphonuclear leucocytes, metamyelocytes, 7, and lymphocytes, 24. A blood smear showed positive sickling, polychromatophilia, and anisocytosis. The urine was negative. The icterus index was 15.

An electrocardiogram suggested pathologic change in the right heart.

Course and Treatment.—By the second hospital day the temperature was 104.2° F. There was tenderness in the right upper quadrant and increased soreness in the abdomen, which was rigid to palpation. Pulse was 140, respirations, 22 to 30. The patient was given plasma and 5 per cent glucose. He developed a gallop rhythm and failing heart. After sickling was demonstrated, the patient was given transfusions. The temperature remained elevated at 103.8° F. rectally. He was placed on 5 per cent glucose because of the liver damage and given continuous oxygen. By the fifth day a precordial friction rub was heard, the liver was increased in size, and the patient remained markedly restless and dyspneic. He expired on the sixth hospital day.

Autopsy Findings.—The essential autopsy findings were as follows:

Heart: The heart weighed 253 Gm. The myocardium was medium red in color and of medium firmness. The wall of the left ventricle measured 15 mm. in thickness, of the right ventricle, 3 mm. The pulmonary valve measured 55 mm. The aorta measured 55 mm. The intima was light yellow in color and smooth. There were small verrucous vegetations along

the line of closure of the mitral valve cusps. The mitral valves were fibrous and somewhat contracted, and the papillary muscles were markedly shortened, thin, and fibrous. The left ventricle was extremely dilated. There was a bread and butter type of fibrinous pericarditis of the pericardial sac, which was fairly easily separated.

Spleen: The spleen weighed 111 grams; the consistency was very firm, the capsule light gray and smooth. On section, the spleen was deep red in color. The follicles were fairly prominent.

Liver: The liver weighed 1,215 Gm. The consistency was firm; the capsule was smooth and glistening. On section, it was medium yellowish red in color.

Microscopic examination.—

Heart: In some of the fibrinous septa, there were aggregations of round cells, suggestive of an old rheumatic process. The red blood cells in the blood vessels showed sickling.

Bone: There were a large number of nucleated red blood cells.

CASE 3.—Negro girl, aged 3 years. Patient entered with complaints of fever for five days, rash five days, and dyspnea and profuse nasal discharge for three days.

Physical Examination.—The temperature was 104° F., pulse 160, respirations 40. The conjunctivae were injected; there was profuse, green, sanguineous nasal discharge. The pharynx was inflamed, and there was a mucoid discharge. The tonsils were hypertrophic and inflamed. The lungs were clear with slight retractions on inspiration in all interspaces. The heart was normal.

Laboratory Findings.—No urinalysis or blood count was reported. A smear of the nasal discharge showed short chain streptococci.

Course.—The patient ran a downhill course and expired two days after admission.

Autopsy Findings.—

Heart: The heart weighed 55 Gm.; both ventricles were dilated; the epicardium and endocardium were delicate; the myocardium was firm and bluish red.

Spleen: The spleen weighed 95 Gm. and measured 13 by 7 by 4 cm. It was large, dark bluish red, and stony hard. On cut section, the spleen was smooth and the follicles small.

Liver: The liver weighed 575 Gm. and was of normal size and configuration. On cut section it showed only slight congestion.

Microscopic findings.—

Heart: The capillaries were congested. There were many Aschoff nodules around the small arteries, consisting of round cells, Anitschkow's cells, and plasma cells.

Spleen: The sinusoids were dilated and crowded with sickle-shaped red blood cells.

Liver: There were focal areas of congestion.

Red blood cells in all organs showed sickling.

SUMMARY

An attempt has been made to ascertain the incidence of sickle-cell anemia concomitant with rheumatic heart disease. Fifty-three autopsies have been performed at Cook County Hospital since 1929 on individuals who gave positive evidence of sickle-cell anemia. Of this group there were three patients who showed concomitant findings of rheumatic heart disease. The incidence was 5.6 per cent.

I wish to thank Dr. I. Pat Bronstein, Associate Professor, Department of Pediatrics, University of Illinois College of Medicine, for his interesting discussion, which stimulated this investigation.

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ERYTHROBLASTOSIS FETALIS ASSOCIATED WITH Rh-POSITIVE MOTHERS

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FOLLOWING close upon Landsteiner and Wiener's¹ discovery of the Rh factor, Levine and his associates² developed the idea of maternal isoimmunization in the pathogenesis of erythroblastosis fetalis, demonstrating the relationship between Rh incompatibility and erythroblastosis fetalis. In over 90 per cent of the cases the father and child were Rh positive and the mother, Rh negative. Clinically, erythroblastosis fetalis is considered as a single disease with three chief recognized forms, called fetal hydrops, icterus gravis, and congenital anemia.

Erythroblastosis fetalis is generally considered as being synonymous with Rh incompatibility and associated with Rh-negative mothers in over 90 per cent of the cases. However, not all cases of erythroblastosis fetalis are caused by the Rh antigen-antibody reaction. On a theoretical basis, incompatibilities can occur from any blood antigen which is present in the father, transmitted to the offspring, and absent in the mother. The Rh subgroups, the Hr factor, and ABO group incompatibilities are possible etiological agents. The M, N, and P factors are apparently not antigenic. Tovey³ gives four reasons why the fetus enjoys protection from the mother's agglutinins in heterospecific pregnancies:

1. There is lack of placental permeability to anti-A or anti-B agglutinins.
2. Fetal plasma neutralizes the A or B antibodies.
3. Fetal erythrocytes are not sufficiently sensitive.
4. The A and B antibodies do not react very well at body temperature.

We are presenting two cases because they were both diagnosed clinically as erythroblastosis fetalis and in both the mothers were Rh positive. Likewise, in both cases the paternal and maternal bloods were identical in Rh groupings, subgroupings, and Rh factor, with the absence of Rh antibodies from the maternal blood.

One infant was diagnosed as having congenital hydrops and died about one-half hour after birth. The Rh, Hr, and ABO groupings of both parents were identical. Antibodies were absent from the maternal blood. We believe that this can be classified as a case of universal edema of the fetus unassociated with erythroblastosis as described by Potter.⁴ The second patient showed jaundice, anemia, and erythroblastosis with no incompatibilities of the Rh or Hr groups. Instead there was an incompatibility of the ABO groups with a high maternal anti-A agglutinin titer.

CASE REPORTS

CASE 1.—The mother was gravida i, para 0; there had been no miscarriages and there was no history of transfusions. The serology was negative. The pregnancy itself was un-

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eventful. The child was born after a prolonged second stage. The scalp was edematous and suture lines were not made out. The extremities were tense and rigid. The head appeared attached to the body. The amniotic fluid was bloody. The child lived about forty minutes. The estimated gestation age was about 8 months. A clinical diagnosis of erythroblastosis fetalis, hydrops type, was made.

An autopsy was performed. Marked edema of the entire body was noted, with edema of the rectus muscle. There were blotchy, bluish red spots over the skin surface. The abdomen was filled with a blood-tinged fluid. There were accumulations of a clear fluid in the pleural cavity, with compression of the lungs. The liver weighed 120 Gm. and the spleen, 12 Gm. There was marked hemorrhage into the soft tissue beneath the scalp, which formed a one centimeter membrane over the calvarium. The sections showed extensive extrahematopoiesis in the liver and small interstitial cellular accumulations in the rectus muscle, probably myeloid metaplasia. Other findings were not significant. The final diagnosis was congenital fetal hydrops, not associated with erythroblastosis. There were extrahematopoietic foci in liver (extensive) and muscle (few), edema of body surfaces and subcutaneous tissues, ascites and bilateral hydrothorax, and bilateral atelectasis.

The mother's and father's blood was sent to Dr. Anna May Young of Cleveland and Dr. Mary Lou Scholl of Columbus, Ohio.

The mother's blood was Type A, Rh₀ positive, Hr positive, MN. The father's blood was Type A, Group Rh₀ positive, Hr positive, M. There were no demonstrable antibodies in the mother's blood, and the maternal and paternal bloods were completely compatible. Fetal blood was not available for examination.

The history, serologic findings, and most of the microscopic sections were sent to Dr. Edith L. Potter in Chicago. She agreed that everything fitted into a diagnosis of fetal hydrops without erythroblastosis except the appearance of the liver. She thought that the amount of erythroblastosis in the liver was probably explainable on the basis of fetal age.

CASE 2.—A 23 year old white woman was admitted to the hospital for her first delivery. The patient had had a normal pregnancy and delivered without difficulty an 8 month male infant with a birth weight of 3 pounds and 12 ounces. The infant had some difficulty in breathing following delivery, respirations were shallow and irregular. The infant's color was pale, and he had a weak cry. He was given alphalobeline, oxygen, Co-amine, and vitamin K intramuscularly, and also mouth to mouth breathing. Twenty-four hours after birth the child became jaundiced and had rigid extremities, and his condition became critical. He was immediately given 20 to 30 c.c. of the father's blood intramuscularly and one ampule of vitamin K every twelve hours intramuscularly. The respirations became irregular and shallow, and cyanosis developed. A diagnosis of erythroblastosis fetalis was made.

Pediatric consultation was obtained. Physical examination of the baby revealed a critically ill infant, jaundiced, and with very shallow, irregular respirations. The liver and spleen were palpable, and the infant was somewhat dehydrated.

The laboratory report showed that the infant was Type A, Rh positive, with a 52 per cent hemoglobin (Sahlb). The mother was Type O, Rh positive. The blood smear of the infant revealed over 100 normoblasts per 100 white cells. The infant was immediately given small Type A Rh negative blood transfusions intravenously (7 to 10 c.c. per pound of body weight). The baby responded well to the transfusions, and his hemoglobin went from 52 per cent to 104 per cent at one time, reaching a stationary point of 80 per cent at the end of twenty seven days. Further laboratory work at this time done by Dr. Mary Lou Scholl of Columbus, Ohio, revealed the following.

Mother: O, Rh positive—Hr positive heterozygous,

Father: A, Rh positive—Hr negative homozygous,

Baby: A, Rh positive—Hr positive heterozygous,

Mother: anti A titer = 1:4,000 (normal 1:64).

The condition of the child remained good until the seventeenth day after birth, at which time the infant started to have frequent bowel movements with mucus and blood. The abdomen became distended and his condition became critical. Surgical consultation entertained the possibility of intussusception, but repeated enemas relieved the condition.

On the forty-second day of life, the infant's hemoglobin dropped to 42 per cent and again Type A Rh-negative blood transfusions were given. Final hemoglobin at time of discharge was 76 per cent.

The child maintained a temperature between 97° and 100° F. throughout his entire stay in the hospital. The baby was followed by the private physician, and the hemoglobin has now been 70 per cent for the past three to four months. The general condition of the child is good, as is his growth and development.

DISCUSSION OF CASES

The diagnosis of fetal hydrops unassociated with erythroblastosis as described by Potter, is supported by the following facts: (1) primiparity of the mother, (2) no history of previous pregnancy or transfusions, (3) Rh-positive mother, (4) absence of antibodies from maternal blood, and (5) identical ABO, Rh, and Hr groupings of mother and father. There was, therefore, no antigenic factor present in the father's blood that was not present in the mother's. The differences in the M and N groups can be discounted as far as antigenicity is concerned. A sixth supporting fact was the compatibility of paternal and maternal blood by direct examination.

The histologic studies left some room for doubt. There was an unusual amount of extrahematopoiesis in the liver, but this probably can be explained on the basis of prematurity. Except for one focus in the rectus muscle (and this was adjacent to an area of hemorrhage), there was no unusual extramedullary hematopoiesis in the other organs.

The etiology of this condition is unknown. A number of cases have been associated with other abnormalities, such as cleft palate and congenital heart disease. The differentiation from true erythroblastosis is important, because the prognosis here as far as future pregnancies are concerned is good.

In our second case, the diagnosis of erythroblastosis unassociated with the Rh factor was supported by the following facts: (1) jaundice and severe anemia in the child, (2) large numbers of erythroblasts and normoblasts in the peripheral blood, (3) presence of large spleen and liver, (4) identical Rh groupings of mother and father, (5) mother was Rh positive, (6) absence of Rh antibodies from maternal blood, (7) father and child were Type A and mother, Type O, and (8) anti-A type of maternal blood was 1:4,000.

GENERAL DISCUSSION

Erythroblastosis associated with an ABO incompatibility was present in nine of 150 infants (6 per cent) seen by Polayes and Ohlbanen⁵ and in two of 100 infants seen by Boorman and his associates.⁶ All mothers were Rh positive. Most babies were Group A. Group B isoimmunizations were very unusual.

Very rarely both Rh and ABO incompatibilities may exist in the same patient. Wiener and his associates⁷ believe that when an Rh-negative woman is exposed to an Rh-positive blood of an incompatible type, the principle of competition of antigens may operate with suppression of the Rh factor.

The mechanism of pathogenesis of erythroblastosis associated with an ABO incompatibility is similar to that when the Rh factor is involved. In the latter,

there is an Rh-positive father and offspring, and an Rh-negative mother. The Rh factor of the fetus acts as a foreign antigen when it gets into the maternal blood stream across the placenta, and sets up an antibody reaction. When the antibodies reach the fetal blood across the placenta, they act on the Rh-positive cells and produce hemolysis. By substituting the Group O mother for the Rh-negative mother, and an A or B fetus for the Rh-positive fetus (or any series of incompatible A, B, O antigens), one can demonstrate the same mechanism.

The surprising feature is not that an ABO incompatibility may lead to erythroblastosis, but that it does not do so more frequently. The factors in the production of erythroblastosis and the protective mechanisms involved are admirably discussed in papers by Boorman and his co-workers,⁶ Tovey,³ Wiener and his associates,⁷ Bryce and her associates,⁸ and Potter.⁹ The main points in the protective theories are as follows:

1. The maternal alpha and beta agglutinins are usually of low titer.
2. The placenta acts as a barrier against these agglutinins, since they are large molecules.
3. There is relative lack of sensitivity of the fetal red blood cells to agglutination. This is probably associated with their incomplete development.
4. Alpha and beta antibodies are absorbed by extracorpuseular group-specific antigens before they get into the fetal blood stream.

Wiener and his associates,⁷ Boorman and his co-workers,⁶ and Smith,¹⁰ found that the majority of infants producing maternal agglutinins were secretors (normally 80 per cent are secretors and 20 per cent, nonsecretors). Isoimmunization was probably brought about by the passage of the soluble group-specific substances across the placenta.

In view of the hypothetical nature of the factors involved in the possible protective mechanism, it is not at all surprising to find conflicting reports on the relationship between maternal titer and fetal injury.

Polayes and Ohlbanen⁵ found that the average anti-A titer of Group O women who had never borne children was 59 (from 20 to 100), and in those who had borne normal Type A children the average was 215 (from 120 to 300). Of the cases of erythroblastosis reported by them, the anti-A titer in maternal blood ranged from 600 to 1,280. Smith¹⁰ recorded a distinct rise in maternal agglutinins in heterospecific pregnancies. In forty out of forty-six pregnancies, there was a rise in titer up to 12,800, with no evidence of harm to the babies. Bryce and her co-workers⁸ found a rise of titer in all cases of ABO incompatibilities in which there was damage to the infant. Boorman and his associates⁶ found anti-B agglutinins incompatible with the fetal red blood cells with titers of 32,000 and 8 million, in two cases of erythroblastosis. In one normal case there was an anti-A titer of 32,000 or over. In sixteen other normal cases, the anti-A and anti-B titers ranged between 56 and 400. Aubert and his associates¹¹ reported one case of erythroblastosis proved by autopsy in which the maternal anti-A titer rose to 16 million. In the case reported by Gruber and his co-workers¹² the anti-B titer was 400.

Boorman and his associates⁶ made the statement that the maternal titer was not the only important thing. It is the effect on the fetus that counts,

and this depends on the permeability of the placenta, the amount of extracorporeal group-specific substance, and probably the other protective factors discussed. The titer was probably the important thing with the Rh incompatibility and the amount of extracorporeal group-specific substances in the ABO incompatibilities.

CONCLUSIONS

1. The clinical diagnosis of erythroblastosis is commonly associated with an Rh incompatibility, occurring in Rh-negative women in over 90 per cent of the cases.

2. Two cases of clinically diagnosed erythroblastosis are presented. In both, the women were Rh-positive with no Rh or Hr incompatibilities.

3. One case was due to an ABO incompatibility.

4. The other case was diagnosed as fetal hydrops unassociated with erythroblastosis fetalis. The diagnosis was established by a thorough serologic study and autopsy. Because of the difference in prognosis as far as future pregnancies are concerned between this and fetal hydrops associated with erythroblastosis, it is important to arrive at a correct diagnosis.

5. A discussion of the immunologic aspect of the ABO incompatibility is presented with reference to the factors involved in the protective mechanism.

We wish to thank Drs. Louis Hait and N. A. Tillman of Lorain, Ohio, for permission to review their cases. We also wish to thank Drs. Mary Lou Scholl of Columbus, Ohio, and Mary Ann Young of Cleveland, Ohio, for performing complete blood examinations and antibody determinations, and Dr. Edith Potter for reviewing the case of fetal hydrops.

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RUPTURE OF LIVER AND SPLEEN IN THE NEWBORN INFANT¹⁰

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THE present series of cases of rupture of the liver or the spleen, or both, will be reported in order to point out a possible cause of these injuries which, if properly understood, might be avoided in some instances.

Rupture of the liver is not a very rare finding at autopsy in newborn infants. Among those who have reported cases and reviewed the subject, Genell,¹ Lundqvist,² Ehlenfest,³ Rogers,⁴ Schmitt,⁵ Silver,⁶ and Henderson⁷ might be mentioned. These and other authors have reported a relatively high incidence of birth trauma to the liver in infants larger than average but have also found it in small, premature infants. This distribution is not surprising and parallels that of cerebral birth injuries. Genell¹ studied the possible mechanisms by which the liver may be injured at birth and assumed that bending and compression of the body are the causes. The former may occur in certain manipulations which are occasionally used in delivery and resuscitation, and result in lacerations extending inward from the surface of the liver. Compression, on the other hand, should produce lesions in the interior of the organ, and Genell suggests that such lesions might be discovered more frequently if the liver of each newborn infant were sectioned carefully at autopsy. McNitt⁸ mentions pressure or torsion of the fetal abdomen, including even gentle ante-partum manipulations. Belohradsky⁹ implicates severe congestion of the liver in asphyxia as a predisposition to rupture, and this possibility is also acknowledged by Henderson.⁷ As an indication of the frequency of birth injury to the liver, Potter's¹⁰ statistical analysis of 2,000 unselected autopsies of newborn and stillborn infants may be mentioned. This series contains twenty-four cases of laceration of the liver. In all instances recorded in the previously mentioned reports, the diagnosis was made at autopsy. To the best of my knowledge, the only cases in which the condition was diagnosed during life and successfully treated are those of Rubovitz¹¹ and Arden.¹² Rogers⁴ suggests abdominal paracentesis for the diagnosis of hemoperitoneum.

Rupture of the spleen is much less common than that of the liver. Lundqvist² found it in one case compared with five cases of ruptured liver. In that one infant the liver was large and showed syphilitic changes. Lundqvist quotes Hedren as stating that rupture of the spleen occurs only in syphilitic infants. In a case recorded by Rhamy,¹³ the spleen weighed 125 Gm., and the underlying condition was diagnosed by several experts either as erythroblastosis or as leukemia. Scott and Bowman,¹⁴ in a review of all cases of rupture of the spleen

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TABLE I SUMMARY OF EIGHT CASES OF RUPTURE OF THE LIVER AND THE SPLEEN

CASE NO.	WEIGHT (GM.)	LENGTH (CM.)	AGE	LIVER			SPLEEN		HISTOLOGY (C. C. — 1 STPH. MAT'D)	FETAL
				WEIGHT (GM.)	AB- NORMAL FETAL TISSUES	DISSECTION	WEIGHT (GM.)	DISSECTION		
1	415	28	12 hr.	20		Laceration, hematomas of both lobes anteriorly	1	-	5	
2	730	32	1 hr.	40		Hematoma at border of left lobe	1	-	5	
3	800	36	Stillborn	43		Subcapsular hematoma at coronary ligament and lower surface rt lobe	1	-	5	
4	1350	42	1½ days	80		Subcapsular tear almost through entire thickness of rt lobe, probably 2 stage rupture	2	-	20	13
5	3140	48.5	Stillborn	145	+	Laceration at edge of left lobe, hematomas on lower surface	10	Laceration at phrenicohepatic lig.	15	5
6	3630	53	13 hr.	215	++	Hematomas at coronary and hepatoduodenal ligaments	38	Laceration at phrenicohepatic lig.	20	6
7	4300	57	27 hr.	137	+	Hematoma on convexity of left lobe	10	Laceration at phrenicohepatic lig.	200	
8	4570	54	Stillborn	347	++	Lacerations at umbilical vein and convexity of left lobe	17	-	20	

in childhood observed in a surgical service over a long period of time, mention none in newborn infants.

The present series of eight cases (Table I) includes five with rupture of the liver, one with rupture of the spleen, and two in which both organs were injured. They were found among autopsies on 121 infants who were stillborn or died during the first three days of life. Cases with hematoma of the liver without hemoperitoneum and those in which rupture had probably occurred after death in utero are not included. The distribution according to size of the infant conforms with that already mentioned. In order to evaluate properly the incidence in infants greater than average size (Cases 6, 7, 8), one must keep in mind that the great majority of all infants examined at autopsy at this hospital are premature. Actually, only sixteen of the 121 infants examined weighed 3,500 Gm. or more.

In two of our patients, the data in Table I should be supplemented by brief notes on the clinical course and autopsy findings.

CASE 4.—This infant was born spontaneously and showed at first no abnormalities. The birth weight was 1,410 Gm. At 32 hours of age, the infant suddenly turned pale and limp after being turned and having the diaper changed. No respiration or heart sounds were present. After artificial respiration, cardiac massage, and stimulants, respiration and heart action started again, but stopped soon. In this patient, the findings recorded in Table I indicate very severe trauma to the liver with a small tear in the capsule and a moderate amount of blood in the peritoneal cavity. In view of the history, these findings are best interpreted as the result of a two-stage rupture, the second stage of which had occurred just before death. This seems to be a fairly typical occurrence, and Potter¹⁵ mentions that infants who suddenly die after bath or feeding often have a ruptured subcapsular hematoma of the liver.

CASE 8.—This was the seventh pregnancy of a 35-year-old mother. Labor was slow but progressive. The head was delivered after fifty-five hours of labor. After this the shoulders were fixed in a transverse position at the spines. The head was rotated to the left, and the left shoulder appeared under the symphysis while a snapping sound was heard. The body was delivered with ease to the level of the umbilicus. At this point some difficulty was encountered. The fetal heart was last heard just before delivery. There was no blood group incompatibility between mother and infant. The data in Table I indicate the very large size of the liver in this patient and the locations of the injuries found at autopsy.

The history of the remaining six infants is irrelevant. In no case was the diagnosis of intra-abdominal hemorrhage made during life.

When one reviews the location of the hematomas and lacerations in these eight patients, several distinct types may be found. One is associated with ligaments inserting in the liver or spleen. This is the case in all three instances of laceration of the spleen; in Cases 3 and 6 hematomas are present at the coronary ligament of the liver; in Case 6, also in the hepatoduodenal ligament; and in Case 8, one of the lacerations has a location suggesting that the umbilical vein cut into the liver tissue. In all these cases, the injury can be



Fig. 1.

Case 1.

- Fig. 1.—The situs of the abdominal organs. The greater part of the liver is dark red in color, and the capsule over it is torn.
- Fig. 2.—View of the cut surface of the liver (slides reversed). The dark portion of the right lobe is almost completely separated from the rest of the liver by a deep cleft.
- Fig. 3.—A microscope section of the border area shows the hemorrhagic and necrotic tissue (corresponding to the dark areas in Figs. 1 and 2) in the upper portion, and the normal tissue with a few small areas of necrosis in the lower portion.

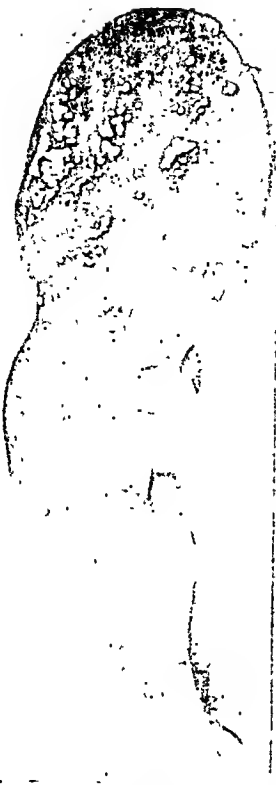


Fig. 3.

explained by a trauma forcing the liver and spleen downward and thus tending to tear these organs off their ligaments.

The location of another group of lacerations on the anterior surface of the liver strongly suggests that the injuries are the result of excessive pressure by the costal margin (Cases 1, 2, 5, 7). This was also found in cases of hematoma without rupture which are not included in the present series. Finally, there are instances in which no specific explanation for the localization of the damage can be given.

Before further discussing the mechanisms by which many of these lacerations may have been caused, a few words should be said about the phrenico-lial ligament. Textbooks of anatomy describe this ligament as inserting at the hilus of the spleen and carrying the splenic vessels. However, examination of the spleen *in situ* in many newborn infants has shown that the ligament frequently inserts not only at the hilus, but also extends in the direction of the lower pole and sometimes even to the convex surface (Fig. 4). This insertion of the ligament in the spleen itself rather than in the tissue of the hilus apparently predisposes to laceration when the spleen is pulled away from its normal location (Figs. 5, 6).



Fig. 1.



Fig. 5.



Fig. 6.

Figs. 1, 5, and 6.—Spleen and adjacent portion of the diaphragm, showing the phrenico-lial ligament in a normal newborn infant (Fig. 4), and in Cases 4 and 5 after laceration of the spleen at the insertion of the ligament (Figs. 5 and 6, respectively).

Search for possible circumstances in which liver or spleen may be pulled or pushed downward to the extent of partially tearing off their ligaments has revealed only one plausible mechanism. In the fetus and newborn infants before the onset of regular air breathing, the diaphragm is at a high level with its domes usually reaching to the third rib or intercostal space. Most of the hollow of the diaphragm is occupied by liver, stomach, and spleen. If the thoracic cage is compressed, these organs are squeezed out of the hollow of the diaphragm and forced downward (Fig. 7). Among the ligaments, the phrenico-lial (*a*) and coronary ligaments (*b*) are obviously under tension when liver and spleen move downward. If the border of the liver is not far from the umbilicus, the umbilical vein (*c*) may cut into the organ when the latter is pushed downward (Case 8). The hepatoduodenal ligament is not likely to be affected

since it runs downward from the liver; yet it showed extensive hemorrhage into its tissue, obviously originating from the liver, in Case 6. Thus, compression of the chest rather than the abdomen explains the majority of the injuries to liver and spleen as found in the present cases, either by direct injury to the anterior surface of the liver (Fig. 7, *e*), or by pushing the organs downward (Fig. 7, *a-d*). On the other hand, those injuries which have no characteristic relationship to ligaments or the costal margin are probably due to a more direct trauma to the liver itself. These cases constitute the minority in our material.

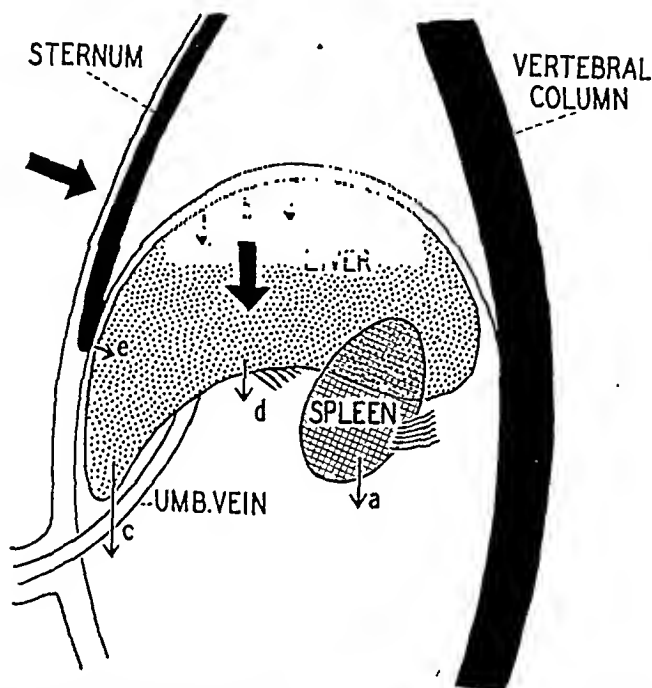


Fig. 7.—Diagram illustrating the effect of compression of the thorax on liver and spleen. As a result, laceration may occur at the following points: *a*, spleen at the phrenicocolic ligament; *b*, liver at the coronary ligament; *c*, the umbilical vein, which may cut into the liver; *d*, liver at the hepatoduodenal ligament; *e*, liver compressed directly by the costal margin.

The relatively high incidence of rupture of liver and spleen in large infants was mentioned above. It should be added that in such children, the liver is often enlarged out of proportion to body size (Cases 6, 8). It is obvious that the mechanism of squeezing organs out of the hollow of the diaphragm will particularly affect a large liver, which may then carry the spleen with it, even if the latter is nearly normal in size. Enlargement of the liver is most commonly found in erythroblastosis and in infants of diabetic mothers. In all three of our infants which were larger than normal, marked hematopoiesis was present in the liver (Cases 6, 7, 8), just as occurs in both erythroblastic infants and in children of diabetic mothers. Clinical investigation did not reveal any of these patients to be an unequivocal example of either of these; yet, it might be well to remember that erythroblastic infants and those of diabetic mothers may be more likely to suffer a birth injury to liver or spleen than others.

SUMMARY

The evaluation of findings in eight newborn infants with birth injuries to liver or spleen or both suggests that pressure on the thorax is an important factor in the production of these lesions. By such pressure, the organs of the upper abdomen are squeezed out of the hollow of the diaphragm, and undue tension on the ligaments of the liver and spleen then produces part of the lesions. Others are the result of direct pressure of the costal margin on the anterior surface of the liver. A minority of the lesions of the liver in the present group of cases are not obviously related to these mechanisms and are probably due to direct trauma.

Large infants and those with a relatively large liver as it occurs in erythroblastosis or in maternal diabetes are more susceptible to injury of liver or spleen than others.

In order to prevent these lesions, not only direct trauma to the abdomen but also pressure on the thorax should be avoided as much as possible.

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CHILDHOOD MANIFESTATIONS OF ALLERGIC ADULTS

PRELUDE TO ALLERGY

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THE growing child from birth through adolescence reveals frequent recurrent manifestations of disharmony with living experiences. Everyone has witnessed in his own family circle occasional fears or tantrums which represent a child's reactions to the frustrations and drives which harass him. These fears and tantrums are useful devices for protecting the child's integrity in a conflicting world. In the physical field, the human organism possesses an equivalent versatility in reacting to various substances which threaten the specificity of its body proteins. The minor expressions of these reactions are often as mild as are the minor tantrums of the problem child. At other times, the manifestations are violent examples of Pirquet's term "allergy" or altered reaction—a boiling-over, not unlike the childhood neuroses. In the management and control of these, pediatricists and allergists face, in the physical field, the same dilemma which pediatricists and psychiatrists encounter in the mental and emotional field.

The cardinal elements of the allergic design are capillary dilatation and permeability, smooth muscle contraction, and edema. These cellular peculiarities may produce variations in function of one or several organs which earlier clinicians were led to classify as diatheses. Some of these classifications parallel what we now call allergies. Pediatric writing reveals much thinking along this line. Most of this literature antedates the modern period of allergic study, but it is nevertheless obvious that the writers were dealing with what we now call allergic characteristics. In 1902, the year of Richet's memorable experiment, Comby,¹ the French pediatricist, described what he called "arthritis." The signs and symptoms are as follows:

1. Catch cold easily.
2. Subject to nosebleed, more common in summer than winter, spring than fall.
3. Symptoms often related to changes in barometer.
4. Hay fever a later development.
5. Often have large tonsils and adenoids and stridorous breathing.
6. Spasmodic tracheobronchitis.
7. Exaggerated dyspnea with moderate bronchitis.
8. Perversion and modification of appetite; food dislikes common; geophagia; pica.
9. Intestinal colic.
10. Regurgitation and other varieties of dyspepsia.
11. Cyclic vomiting.
12. Cephalalgia.

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While some of the signs and symptoms recorded by Comby seem irrelevant to allergy, the major characteristics of arthritism are unmistakably those of allergic children. Czerny, the renowned German pediatricist, classified a group of symptoms under the heading of "exudative diathesis" (Table I), another illustration of a common pattern seen in allergic children.

TABLE I. EXUDATIVE DIATHESIS OF CZERNY

	PRIMARY SIGNS	SECONDARY SIGNS	ASSOCIATED SIGNS AND SYMPTOMS
Skin	Intertrigo Seborrhea Cradle cap	Eczema Impetigo	Itching Restlessness Disturbed sleep Fears
Mucous membranes	Desquamation and swelling of various organs	Exudative diseases of pharynx and G.I. tract Coryza Laryngitis Bronchitis Blepharitis Phlyctenules Vulvovaginitis	Cough Vomiting Colic Constipation Diarrhea Hay fever Spasmodic croup Asthma Blepharospasm Dysuria Enuresis

The correct interpretation of allergic signs and symptoms may not be reached until long after the symptoms have occurred. In this respect, the single incidents of an allergic history may be not unlike the single takes of a moving picture, in which even the actors are unable to recognize understandable continuity. Each incident begins to make sense only as the whole story is unfolded. Aside from the inadequacies of the story as related by a parent—and there are many—appraisals will differ considerably, depending on what scenes or manifestations the appraiser is willing to accept as part of the story or pattern.

Allergic manifestations generally, and particularly in the child, present many unusual variations in intensity and character. These variations are thought to represent differences in capacity for reacting as modified by genetics, age, and fortuitous differences in environmental experience. Some are easily definable as specific reactions to known allergens; many more seem not unlike the phenomena described by Selye² as elements of a general adaptation syndrome, additionally complicated by psychogenic factors. The clue to an allergic diagnosis may therefore be obscured not alone by the wide range of allergic manifestations, but by a variety of complicating mechanisms which accompany biologic phenomena.

For the past few years, I have been reviewing the records of former pediatric patients, now grown men and women. After determining by phone or letter which of these adults had developed allergic symptoms as recognized by their families, clinical inventories were made of their childhood characteristics as recorded in their histories, in an effort to discern a childhood pattern common to those who became allergic subjects. Many of the listed characteristics may lack immunologic validity—that is to say, an antigen-antibody mechanism was not demonstrated. The same characteristics, however, occur frequently enough

in allergic subjects to lend them more than an accidental significance and to form a common pattern. Despite the hematologic discrepancies, "the coat is the coat of Joseph." Although many of the patients used as the basis of this report were easily recognizable as allergic subjects early in life, many others presented no clinical signs regarded as allergically relevant during their childhood. The following signs and symptoms are not necessarily diagnostic signs of allergy. They are the things which happened to allergic subjects in their early childhood. A review of these signs and symptoms shows many characteristics which are by their very nature major allergic evidences. Many others have not been generally recognized as having validity in the early recognition of the allergic personality.

Allergic Characteristics

Digestive Signs and Symptoms

1. Pylorospasm.
2. Enterospasm.
3. Hyperperistalsis—recurrent vomiting, cyclic vomiting, willful vomiting, neurotic vomiting, facility at gagging.
4. Pyloric stenosis.
5. Recurrent abdominal pain (during or between meals), finicky eater.
6. Hypotrophy.

Respiratory Signs and Symptoms

1. Nasal snorting, snuffling, or stuffiness. (Difficulty in breathing, peculiar breathing, fills up with mucus.)
2. Exudative throat (excessive mucus).
3. Congenital stridor.
4. Abnormal frequency of colds.
5. Early adenoid trouble.
6. Allergic salute.
7. Open mouth.
8. Recessive mandible.
9. Nosebleeds.
10. Turgescence mucosa.
11. Excoriated nostrils.
12. Nasal eosinophilia.
13. Hay fever.
14. Recurrent bronchitis.
15. Asthma.
16. Thymic asthma.

Dermatologic Signs and Symptoms

1. Dermatitis neonatorum.
2. Seborrheic dermatitis.
3. Infantile eczema.
4. Urticaria.
5. Atopic rashes. Excessive reactions to sun, insects, dyestuffs in clothing, heat and cold, wool, rubber pants.
6. Dermographism.
7. Canker sores—cheilitis.
8. Vasomotor lability—localized cyanosis of extremities.
9. Hydrolability.
10. Angiospastic pseudoanemia.

Ophthalmic Signs and Symptoms

1. Blepharitis.
2. Recurrent styes or chalazia.

3. Angioneurotic edema.
4. Vernal conjunctivitis.
5. Conjunctivitis—general or focal.
6. Localized pollinosis.
7. Itching—rubbing.

Genitourinary Signs and Symptoms

1. Vaginitis or vulvitis nonspecific.
2. Enuresis.
3. Pruritus.
4. Hydrocele.

Neuromuscular and Psychosomatic Signs and Symptoms

1. Fatigability increased.
2. Night restlessness or fears.
3. Compulsion neuroses.
4. Leg pains.
5. Blue hands and feet.
6. Migraine.
7. "Alarm reactions."
8. Convulsive seizures.

GASTROINTESTINAL CHARACTERISTICS

While the common occurrence of gastrointestinal allergy is well known, the unusual frequency of a disturbed digestive tract in the first few months of life in allergic persons has not been emphasized. In the present study, the occurrence of frequent stools, or loose, foamy, or frothy stools, and hyperperistalsis with or without pylorospasm, were the most common initial manifestations of the allergic constitution in the first three months of life. The hyperperistalsis often showed itself in the first few days of life, accounting for such clinical descriptions as "dyspepsia of the newborn." These symptoms occurred when the infant was a few weeks old and/or after the ingestion of particular foods. In some, the occurrence of temporary periods of improvement followed seemingly unrelated diet changes. Pain may or may not have accompanied the hyperperistalsis. When pain occurred, its severity varied from a mild type, the "under-done" baby of Brenemann, with rhythmical recurrences of discomfort which lent themselves to minor therapeutic measures, to colic severe enough to warrant repeated sedation. The descriptive term "all gut and squall" applies to infants with such severe abdominal pain. While it is not unlikely that some of these infants earned their places in such diagnostic pigeon holes as "under-feeding," "overfeeding," "neuropathic diathesis," "hypertonic infant," "enterospasm," "fat indigestion," and "carbohydrate intolerance," many of them continued discomforted and their pediatricist dissatisfied despite placement in these categories. Among the infancy records of my series, I find such notations as "Breast milk not agreeing," or "Mother reports that infant gags and cuts up generally," or "Screaming spells, vomiting, mucus in stools, fusses after feeding"—this last, in a child who later ran the gamut of allergic experience including a Löffler's syndrome.

In children past infancy, the most significant digestive symptom other than recurrent abdominal pain attacks was an unusual facility at vomiting. The most trifling provocations might elicit gag reflexes, which were easily conditioned by

psychogene factors. Among this group is the record of a fastidious 4-year-old who, after finishing his meal and quietly announcing "I have to go to the bathroom," would then empty the contents of his stomach into the toilet bowl. A few years later, this child was a major respiratory allergy patient. Recurrent vomiting and cyclic vomiting, a more common diagnosis in former years, undoubtedly belong in this category. The alleged relationship of pyloric stenosis to the allergic constitution finds confirmation in this study.

RESPIRATORY CHARACTERISTICS

Nasal snuffling, snorting, or stuffiness is not uncommonly witnessed in the first few weeks of life. Eliminating those instances explainable by small nasal passages or other anomalies of structure, or explainable by regurgitation of milk curds into the posterior nares, we nevertheless see a considerable number of patients with respiratory symptoms for which there is no obvious explanation. The symptoms appear frequently in the early histories of allergic persons. On clinical records, I find notations such as "difficulty in breathing," "peculiar breathing," "fills up with mucus." An allergic parentage suggests a common etiology for parent and child symptoms. Children with such symptoms are frequently the subjects of early adenoidectomy, an operation which, in the allergic child, will need repeating in later years.

The two most commonly used pediatric texts fail to mention epistaxis as a symptom of allergy. Its frequency in the group of patients studied leads me to believe that, eliminating trauma and blood dyscrasias, epistaxis is more likely due to allergy than to any other cause. As such it may appear even in infancy, long before major allergic signs become apparent.

STATUS THYMICO-LYMPHATICUS

The pathologic relevancy of status thymico-lymphaticus has been a controversial subject for the past two decades. It is now generally believed that simple thymic enlargement is not in itself a cause of so-called thymic symptoms. Sudden deaths without discoverable significant anatomic changes continue to puzzle pediatricists and pathologists. In many patients who die suddenly, a complete clinical inventory often reveals characteristics identified with the hypersensitive state of one or more organs, for which Bohrod³ proposed the term "sudden death in the hyper-reactor state." Recent investigations have shown the necessity for increased adrenal cortical hormones for survival when the animal organism is exposed to various insults or damage. It has also been demonstrated that excitation of the autonomic nervous system and the release of epinephrine play a significant part in the availability of cortical hormones at these times. Although the common denominator responsible for these defense mechanisms has not been established, it has been adequately demonstrated that the thymus and adrenal play significant roles. This is also dramatically illustrated by Selye's studies on the adaptation syndrome, in which he showed that rapid involution of the thymus and lymph glands with a hyperplasia of the adrenal cortex occur as cardinal features of the so-called "alarm reaction." While Selye's theory has to do with reactions evoked by sudden exposure to nonspecific

stimuli, clinically similar reactions do occur in allergic subjects without demonstrable specific causes. It would be difficult to distinguish between specific and nonspecific causes in the infant organism, whose immature immunologic mechanisms hamper its ability to acquire resistance to stress.

Selye's hypothesis would explain many of the heretofore inexplicable sudden deaths in infants of allergic families, as well as the less critical cases in which collapse occurs without known specific damage or insult. That there is a tie-up between these basic physiologic responses and allergic manifestations has been suggested by numerous observations, as for example by Aldrich's⁴ study of the relationship between enlarged thymus, pylorospasm, and vagotonia. The observations by Carr⁵ on status thymico-asthmaticus, and by Waldbott⁶ on the similarity of the pathologic findings in necropsies of patients with anaphylaxis and asthma, lend credence to the supposition that this relationship is a significant one.

Although it is difficult to evaluate the importance of thymic enlargement as reported roentgenologically in the past three decades, the curious fact remains that an unusually high percentage of those infants in this study on whom the diagnosis of enlarged thymus was made twenty years ago are now the subjects of major allergy.

The varied manifestations of allergic phenomena may be compared to a symphonic pattern in which the respective episodes present themselves in different arrangements, now emphasized by one set of instruments, now by another. The early characteristics represent the prelude to a pattern often not completely developed as a major theme until later life. Pediatricists by successive chronological experiences with otherwise normal children may learn to evaluate the interrelationship of many of the physiologic phenomena now seemingly unrelated, and increase our understanding of the disease patterns in allergic persons.

SUMMARY

1. The allergic design or pattern often begins in infancy.
2. Many of the characteristics of the allergic pattern have long been recognized by pediatricists and classified as "exudative diathesis" and "arthritis."
3. A knowledge of the early characteristics of the allergic constitution permits a possible interpretation of many of the symptoms and signs of allergy long before major signs have developed.
4. Attention is called to a few less commonly recognized manifestations in the childhood prelude to allergy.

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PREVENTIVE ORTHOPEDICS IN THE TREATMENT OF POLIOMYELITIS

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POLIOMYELITIS at its onset has the characteristics of an acute infectious disease. The attention of the pediatric or medical clinician is invaluable in preserving life and relieving suffering. Unlike most infectious diseases, poliomyelitis tends to develop permanent aftereffects. The principal observable effects are muscular paralysis and skeletal deformity. The interest which has been centered on weakness or paralysis has tended to obscure the gravity of the problem of deformity. Crippling deformities have been a common aftermath of the disease, often not appearing for months or years after the acute attack. Clinical observations recently presented¹ support the view that poliomyelitis attacks the muscle and fascial tissues directly, in addition to the effect of the disease upon the nervous system.

The suggestion that deformities arise directly from disease of the peripheral tissues as part of the acute illness implies the possibility that treatment of the peripheral tissues may reduce or prevent deformity. The underlying cause of deformity has been one of the primary studies in a series of 1,775 patients which have come under the care of this clinic since 1940. The practical aspects of relief and prevention of deformity by treatment of the affected peripheral tissues in this large series of cases is the subject of this presentation.

The patients were admitted with acute poliomyelitis during the various poliomyelitis seasons, beginning in 1940 and extending through 1946, and have been closely followed. Thus, the early aspects of the disease as well as the late effects in the treated patients have been scrutinized.

A serious epidemic of poliomyelitis struck Minnesota in 1946 and provided an opportunity to study the effect of the disease upon the peripheral tissues of 1,125 patients treated in that single year. A mortality of 6 per cent (68 patients) indicates that the disease in 1946 was not mild, but was at least of average severity. In 65.4 per cent (736) of the patients, there was evidence of muscle weakness or paralysis at the height of the disease, but 34.6 per cent (389) of the patients showed no muscle weakness or paralysis at any stage. In every patient in the acute stage it was possible to demonstrate that tissues in the various peripheral parts were involved in a condition of spasm, marked usually by pain and sensitivity.² Muscles in spasm were shortening, and in many of these acutely ill patients incipient deformities were already being produced by the shortening muscles. (See Table I).

The general plan of management³ which was carried out in 1946, as in the previous years, was to hospitalize every patient until spasm and muscle

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TABLE I. INCIPIENT DEFORMITIES FROM MUSCLE SPASM AT THE HEIGHT OF THE DISEASE IN 1,057 SURVIVING PATIENTS WITH ACUTE CASES OF POLIOMYELITIS OF ALL TYPES FROM THE 1946 EPIDEMIC IN MINNESOTA

DEFORMITY	NUMBER OF DEFORMITIES
Torticollis	6
Scoliosis	19
Lordosis	43
Cupped shoulder	25
Tilted pelvis (apparent leg shortening or lengthening)	72
Leg torsion	63
Flexed hip	19
Flexed knee	33
Equinus foot	14
Varus foot	17
Valgus foot	8
Cavus foot	33
Other deformities	43
Total deformities	395

shortening had been overcome and each patient had also been retrained as thoroughly as possible in the normal motor patterns. Treatment of the peripheral tissues consisted primarily of complete rest in bed with prompt and intensive application of moist heat to all areas affected by spasm. As pain and sensitivity disappeared, gentle manipulation and manual release of the shortened tissues was used where necessary in conjunction with the moist heat. Incipient deformities from muscle shortening responded to this treatment as spasm was overcome. Nine of the patients from the 1946 series remain hospitalized for early deformity at the time of this report, but eventual relief can reasonably be expected, on the basis of past experience, by further treatment of these severely affected patients. A possible exception is that of a 6-year-old boy with scoliosis from marked spasm of the spinal muscles, occurring early in the acute stage of the disease and which has responded poorly. The distortions still present, but under treatment, are: four patients with scoliosis, two patients with lordosis, two patients with equinus foot, and one patient with varus foot. At this time, more than a full year after the epidemic, 1,048 of the 1,057 surviving patients are free of gross deformities.

Every patient has been treated for spasm in order to avoid tissue fibrosis and contractures, which have been a cause of late deformity in the growing child. The tendency for contracture of the fascia lata and iliotibial band of the thigh has been particularly vexing in the past and has been a common source of late-appearing deformity. Prevention of future deformity depends apparently upon the successful relief of spasm.

The period of hospitalization of the 1,057 surviving patients of the 1946 epidemic averaged twenty-one days for the thirty-three patients with abortive cases (those with clinical symptoms other than paralysis, but having a normal spinal fluid cell count); twenty-three days for the 356 nonparalytic patients; and will average from two to fourteen months for the paralytic patients, depending upon the severity of the attack. It is estimated that nine patients will require a stay of two years.

Muscle spasm as well as attendant deformity were not found to be confined to the paralytic patient. Spasm is usually more severe and more difficult to

relieve in the paralytic type of case. This is indicated in part by the increased time required for adequate treatment of the paralytic patient. The greater frequency of deformity in the paralytic case undoubtedly has led to the belief that deformities arose from paralysis. Incipient deformities in the series presented here responded to treatment of the peripheral tissues in the paralytic as well as the nonparalytic patients. Once relieved, the deformities have not recurred in spite of weakness and muscle imbalance present in the paralytic patients. New deformities have not developed in the patients who have completed treatment. These observations provide evidence that disease in the peripheral tissues rather than the unbalanced pull of muscles causes deformity. Two representative case histories from the 1946 series reported in this paper illustrate this point.

CASE REPORTS

CASE 1—R. N., an 8 year old boy, became ill July 27, 1946

Diagnosis—Poliomyelitis, acute, paralytic type.

Spinal Fluid Examination—Cells 90 per cubic millimeter; protein 75 mg. per cent

Physical Examination—At the height of the disease there was spasm of the neck, back, hamstring, and calf muscles, and shortening of the iliotibial band and plantar fascia. The incipient deformities of scoliosis, pes varus, and pes cavus were evident. The right arm and right leg were mildly weakened, the left leg was completely paralyzed, and the back and abdomen were severely paralyzed at the height of the disease.

Outcome—Aug. 25, 1947, when the patient was discharged, walking, after 394 days of hospitalization, the muscle shortness was relieved. The left leg and abdomen were still severely paralyzed. There were no deformities at the time of discharge. On Feb. 1, 1948, examination showed paralysis of the left leg and abdomen still present. No deformities have developed. No apparatus is worn. The incipient spinal deformity has been relieved in spite of permanent residual paralysis of the abdomen.

CASE 2—R. R., a 14 year old boy, became ill on Aug. 3, 1946

Diagnosis—Poliomyelitis, acute, nonparalytic type

Spinal Fluid Examination—Cells 62 per cubic millimeter; protein 65 mg. per cent.

Physical Examination—At the height of the disease there was spasm of the neck, back, hamstring, calf, and quadratus lumborum muscles, and shortening of the iliotibial band of the thighs. The incipient deformities present were: tilted pelvis with lumbar scoliosis, an apparent right leg shortening, and a right heel inversion. This patient at no stage of the disease showed any evidence of muscle weakness or paralysis.

Outcome—On Aug. 30, 1946, when the patient was discharged after twenty seven days of hospitalization and treatment to the peripheral tissues, all muscles were of full length and there was no evidence of deformity. No paralysis was present. On Feb. 1, 1948, examination showed a fully recovered patient. No deformities or paralysis were present.

Experience with the 650 patients admitted from 1940 through 1945 shows that gross late deformities have not occurred in the treated patients. Growth in length of limbs affected by the disease has proceeded satisfactorily. Retardation of growth, noticed in the past, has apparently been due to shortened muscles.

No operations have been performed or are known to have been applied to any of the patients. It is possible that cases may appear where function of a part can be improved by transplantation of a muscle, but no practical instance has so far arisen.

Scoliosis has been kept to a minimum. This has been most satisfying in view of the seriousness of spinal deformity and its frequency of occurrence in the past. Colonna and Vom Saal⁴ reported the incidence of scoliosis to be 30 per cent in a series of 500 chronic, paralytic cases of poliomyelitis. There are three instances of gross permanent scoliosis in the 650 patients treated in this clinic from 1940 through 1945. All occurred in the acute stage of the disease and could not be relieved. These patients are worthy of note.

Patient D. L., a young boy, was admitted in October, 1944, at the age of 13 years, with severe spasm affecting particularly the back and legs, and with arms extensively paralyzed. After 572 days of hospitalization he was discharged, but he retained at that time moderate back stiffness and a minimal scoliosis that could not be relieved in spite of intensive treatment to the peripheral structures. He is examined periodically, and while the scoliosis eventually showed a 2-inch deviation of the spine it is not progressing in this boy, who is now 17 years of age.

Two of the young patients just mentioned are girl cousins and were both admitted to this clinic in November, 1945, with severe paralytic type of poliomyelitis. Spasm was extensive throughout the body and was particularly painful. Patient D. D. had incipient right mid-dorsal scoliosis early in the illness but did not respond to intensive treatment. The patient was discharged after 255 days of hospitalization in the belief that the scoliosis might have antedated the poliomyelitis. Within six months from the time of discharge the scoliosis had become much more severe, indicating that it was, after all, poliomyelitic in origin. The patient was readmitted to the hospital for 198 days of further treatment. The scoliosis is still present ($2\frac{1}{2}$ inch deviation of the spine) and cannot be relieved. Patient V. D. developed a left lumbar scoliosis in the acute stage of the disease, due to severe painful spasm of the right spinal and abdominal muscles. The scoliosis has remained minimal ($\frac{7}{8}$ inch deviation of the spine) and appears nonprogressive, but it has not been possible to relieve the muscle shortening causing the scoliosis in 483 days of hospitalization. Another cousin, C. D. (sister of D. D.), was hospitalized with nonparalytic poliomyelitis at the same time as the other two. This patient developed an incipient lumbar scoliosis due to shortening of the quadratus lumborum muscle. The condition was relieved after thirty-one days of hospitalization and has not recurred in the fourteen months since the patient was discharged. It is believed that the two cases of permanent spinal deformity in these cousins resulted from the extremely severe nature of the spasm, as both patients experienced excruciating pain in the acute stage.

The symptoms of disease in the peripheral tissues have been recorded by many observers. Lovett⁵ recognized that the peripheral tissues were tender in the acute stage of poliomyelitis, but from his writings he did not apparently connect this fact with deformity. Ober^{6, 7} pointed out that there was pain deep in muscles in poliomyelitis which was productive of deformity. Miss Kenny was first in establishing muscle spasm as a distinct entity in the disease, and at one time⁸ explained this condition as due to a zone of irritation in the spinal cord. Subsequent investigation¹ indicates that the peripheral tissues of the body

are directly assaulted by the malady. The painful muscles are diseased and shorten themselves if unattended. These observations provide a reasonable clue to the major problem of deformity in poliomyelitis.

Paralysis or motor denervation of muscle is a feature of poliomyelitis. The evidence is convincing that the disease destroys anterior horn cells of the spinal cord in some cases. There is presently no known method of resurrecting these dead nerve cells; therefore, weakness or paralysis must be accepted as permanent in patients exhibiting residually this condition. The management of paralysis requires its own techniques. No clinical or experimental proof has ever been reported to show that deformities arise directly from muscular paralysis or unbalanced muscle pull.

The orthopedic surgeon is concerned with the preservation of structure as well as function of the locomotor system of the body. Poliomyelitis deformities are crippling in themselves, and they add disability to the paralytic patient. The past role of the orthopedic surgeon in poliomyelitis has been largely to correct chronic deformities and to aid the recovery of muscle function through reparative or surgical means. Prevention of aftereffects of disease is a basic principle in orthopedic surgery as it is in the entire field of medicine. From the beginning of poliomyelitis, the orthopedic surgeon and the pediatric or medical clinician working together must be on the alert for prevention and relief of contractures and deformities arising from disease of the peripheral tissues.

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Case Reports

DIAGNOSIS AND TREATMENT OF PANCREATIC CYSTS IN CHILDREN WITH REPORT OF A CASE

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SOLITARY cyst of the pancreas, rare in adults, is so exceedingly rare in children as to be almost a collector's item. Moynihan,¹ writing in 1902, noted that of Korte's collection of 121 cases in 1898, only two were in children: Richardson's² case in a 14-month-old infant, and Shattuck's³ case in a 13-month-old infant in whom the tumor had been noticed at birth. Telling and Dobson⁴ reported a case in an infant in 1909. Eha,⁵ in 1922, reported a case in a child in which the cyst was composed of two distinct sacs. His patient was a 5-month-old female infant. The cyst was 9 cm. in diameter, weighed 99 Gm. and was completely excised at operation. Judd and his associates⁶ mentioned the case of Railton,⁷ reported in 1896, in a 6-month-old infant. Judd reviewed forty-seven cases seen at the Mayo Clinic from 1921 to 1930, occurring in persons between the ages of 20 and 72 years. Drennan⁸ reported a case in a child in 1922. Friedenwald and Cullen⁹ in 1926 reported seven cases of pancreatic cyst from the Johns Hopkins Hospital, including Lewis' case, that of an infant 16 months of age, in whom the cyst was of large size, containing 750 c.c. of fluid. This cyst was treated by incision and drainage, and marsupialization of the cyst to the abdominal wall.

The case here presented is that of a 6-month-old infant with, relatively, a very large cyst, which none the less was susceptible to extirpation.

CASE REPORT

J. M., aged 6 months, was admitted to Bronson Methodist Hospital in Kalamazoo on Nov. 27, 1947, because of abdominal distention with fever and vomiting. He had had a cold for three days prior to admission and had vomited once the day before admission, but abdominal distention was not noted by the parents until the day of admission, when he again vomited. On close questioning it developed that the infant had had an episode of distention and emesis at the age of one month, but it was of short duration and self-limited. Delivery was normal following an uncomplicated full-term pregnancy, there was no history of trauma at birth, and the neonatal period was normal. Feeding and developmental history were normal. The family history was entirely noncontributory; there was one sibling, living and well.

Examination on admission revealed a white male infant of size and appearance commensurate with the stated age. The weight was 17 pounds, 9 ounces. The rectal temperature was 102.6° F., blood pressure 94/60, pulse 140, and respirations 44. The skin was warm and dry with normal turgor, but slightly pale. There was no palpable lymphadenopathy. The head was of normal contour, and palpation revealed no abnormal defects in the skull, nor was a bruit heard over the skull. There was a profuse mucopurulent nasal discharge. The tongue was coated with greenish yellow matter. The posterior pharynx showed

only mild injection. The ears were normal. Extraocular movements were apparently normal, pupillary reflexes were active, and ophthalmoscopic examination revealed normal fundi. Respirations were chiefly thoracic, and the chest was nearly fixed in inspiration. Respiratory movement was abnormally slight, but the lung fields were clear to auscultation and percussion. Examination of the heart was essentially negative, though there appeared to be slight enlargement to the left. The abdomen was markedly distended, and the diaphragm was elevated. A tympanic percussion note was marked over the entire right half of the abdomen, but the note was definitely dull on the left side, with a rather sharp line of demarcation approximately midline. Occasional borborygmus was audible over the right side. The liver was not palpable on the right. Palpation of the left half of the abdomen revealed a cystic mass occupying almost the entire left side; the mass was smooth, extended almost to the floor of the pelvis, and was slightly tender. A definite border could not be felt in any direction. The bladder was not distended. No other masses were felt. The mass was not palpable on rectal examination. The external genitalia and the extremities were normal. Tendon reflexes were normal; abdominal reflexes were absent.

Laboratory Data.—On admission, hemoglobin was 8.2 Gm., the red blood count 3.43 million, and the white blood count 15,300 with 80 per cent neutrophils, 19 per cent lymphocytes, 1 per cent monocytes. Urinalysis was normal except for 4 plus acetone. Blood sugar was 63.7 mg. per cent, the carbon dioxide combining power was 36 volumes per cent, total protein 5.8 Gm. per cent, the albumin-globulin ratio 1.5. Unfortunately, a serum amylase determination was not obtained. However the serum amylase level eight days postoperatively was 144.1 mg. glucose per 100 ml. blood serum, which is within normal limits.

Possible diagnoses considered at this time were enteric cyst, mesenteric cyst, omental cyst, renal cyst, adrenal cyst, hepatic cyst, splenic tumor, pancreatic cyst, and cyst of the retroperitoneal lymphoid tissue, with the possibility that in any case the mass might be malignant with cystic degeneration.

Roentgenograms.—

Chest: November 27—Moderate enlargement of the heart to the left, with prominence of the left auricle, and pulmonary artery shadow. Lung fields clear. Both leaves of the diaphragm are quite high.

Abdomen: November 27—Minimal distention of small and large bowel and stomach. Large soft tissue mass occupying the posterior half of the left abdomen. Practically all of the intestinal shadows are in the right half of the abdomen.

I. V. Pyelogram: November 28—Good concentration of the dye by both kidneys. Slight dilatation of the left renal pelvis, probably due to extrinsic pressure on the lower left ureter.

Barium enema: November 28—Colon lies mainly anterior and in the right abdomen.

Impression: Extra-alimentary, extrarenal tumor.

Course.—The temperature responded fairly well to parenteral fluids and penicillin, but occasionally rose to 103° F. during the preoperative course. Distention was considerably relieved by Wangenstein drainage. Fluid and nutritional requirements were maintained by intravenous and subcutaneous infusions of glucose, Amigen, and vitamins. The patient received whole blood transfusions of 100 c.c. on the second, 45 c.c. on the third, and 100 c.c. on the fourth hospital days. On the fifth day the hemoglobin was 12.4 Gm., the red blood count 3.94 million, the white blood count 21,000, with 75 per cent neutrophils and 25 per cent lymphocytes.

On Dec. 2, 1947, the sixth hospital day, the patient was taken to the operating room, continuous intravenous drip started by cut-down on the saphenous vein, and, under open drop ether anesthesia, the cyst removed. Through a transverse incision above the umbilicus the operator first dissected the retro-peritoneal space on the left side, back almost to the vertebrae, without encountering the tumor. The peritoneum was then opened, and the cyst, about 16 cm. in diameter, filled the incision. The cyst was enveloped in the gastrocolic ligament, which was drawn taut over its surface. The stomach was displaced upward, and the colon forward, down, and to the right by the cyst. The wall was loosely adherent to the stomach anteriorly and to the duodenum posteriorly. The pedicle was quite small, and it was possible to remove the cyst intact by ligation of the pedicle. It was found that most of the body of the pancreas was removed with the cyst, leaving the tail and the head. A soft rubber drain was placed through a stab wound low on the left side, and the operative incision was closed. The patient received 200 c.c. of whole blood during the operation and the next twelve hours.

The duodenal drainage was continued for two days postoperatively, and was not necessary after that time. The wound drained yellow and then yellowish green fluid for one week after operation; then the drain was removed, and the stab wound healed readily. The postoperative course was essentially uncomplicated except for a temperature rise to 102.8° F. on two consecutive days twelve days after the operation, but signs of an upper respiratory infection were found at that time, and the temperature responded promptly to penicillin and symptomatic therapy. Blood sugar determination on December 10 was 82.9 mg. per cent. The abdomen remained flat, and the infant was discharged two weeks after operation, in good condition, taking his feedings well. The weight at discharge was 15 pounds, 14 ounces.

Pathology.—The moderately tense cyst, 16 cm. in diameter, contained 1,000 c.c. of cloudy yellow fluid. The cyst was unilocular. The wall was soft, flexible, 2 to 4 mm. thick, and contained two soft lymph nodes 7 mm. in diameter in the subserosa of the portion which had been attached near the tail of the pancreas. A sheet of ragged turbid fibrin clung to the inner surface of the posterior wall. Microscopically, the cyst wall was found to have no epithelial lining. All parts of the wall showed a hyaline fibrous tissue structure, with varying degrees of edema and lymphocytic infiltration, and remnants of pancreatic structure. The pedicles were found to be pancreatic tissue with excessive fibrous stroma and dilated small ducts. The specimens of pancreatic tissue, taken separately at operation, showed a few islets and marked increase of fibrous stroma, with lymphocystic infiltration. The cyst fluid contained many neutrophils and some red blood cells, but no organisms, few cholesterol crystals. Amylase was present in a concentration a little greater than that normally present in saliva. Trypsin was not found.

Pathologic diagnosis: Pancreatic cyst, possibly of inflammatory origin. Pancreatic fibrosis, possibly related to a general fibrocystic disease of the pancreas.

DISCUSSION

The classification of pancreatic cysts, clearly stated by Moynihan¹⁰ and re-emphasized by Mayo-Robson and Cammidge¹¹ in their monograph on the pancreas, has since been subjected to considerable muddling, and has suffered in passage.

Classification of Pancreatic Cysts.—

1. Retention cyst, due to obstruction in the pancreatic duct, smaller ducts, or acini.

2. Proliferation cysts (cystadenoma and cystepithelioma). Castleman¹² prefers the term cystoma to cystadenoma, because he does not believe there is real formation of glands in these tumors.

3. Congenital cystic disease.

4. Hydatid disease, or parasitic cysts (echinococcus cysts).

5. Pseudocysts, including Moynihan's hemorrhagic cysts, all of which are produced by trauma or degenerative changes of the interstitial tissue of the pancreas. They are distinguished from "true" cysts in that they are not within the substance of the pancreas but lie outside of the pancreas, usually in the lesser omental sac or the gastrocolic ligament. They have no epithelial lining. They are frequently preceded or accompanied by acute or chronic pancreatitis, or hemorrhagic pancreatitis.

6. Dermoid cysts of the pancreas (added by Primrose¹³).

Pathologically, the first three types are "true" cysts and the last three are "false" cysts. However, such a division is of little value from the therapeutic point of view.

Symptoms.—In infancy the symptom that brings the patient to the physician most frequently is the abdominal enlargement; a palpable tumor was present in 114 of Korte's¹⁴ 121 cases. Persistent vomiting and loss of appetite—signs of obstruction, partial or complete—are even more striking, but usually occur later, when the size of the cyst is sufficient to cause obstruction by compression of the small intestine. In our case the parents of the infant having noticed any abnormal enlargement until a day or two before the infant was brought to our attention, but this was more probably on account of parental ineptitude than any sudden increase in size of the cyst, as the fluid contained in this cyst was not grossly bloody, and the blood supply of the cyst wall was well adapted to the size of the cyst at the time of operation. While precursory or concomitant conditions of the pancreas may give rise to signs of disturbed pancreatic function, symptoms of pancreatic cyst per se are due to a mechanical disturbance of neighboring viscera rather than to alterations in the pancreas itself.¹⁵

Diagnosis is based on enlargement of the abdomen, with or without signs of intestinal obstruction; the exculpation of other intra-abdominal cysts, chiefly by roentgenography; and by the characteristic roentgenologic findings of pancreatic cyst. In pseudocyst, in addition, the serum amylase level is frequently elevated above normal.¹⁶ Case¹⁷ has given us an excellent survey of the roentgenologic aspects of pancreatic cyst, to which the reader is referred for a comprehensive handling of this matter. Suffice it to say that intravenous pyelography will ordinarily reveal a normal urinary tract, and that gastrointestinal series of x-ray pictures following barium meal and barium enema will reveal displacement of the stomach upward or forward (in a smaller cyst), and of the colon and small intestines downward and to the right side of the abdomen, by a mass of homogeneous opacity with smooth round borders. Gastric pneumograms are also of value. Differential diagnosis in children should exclude adrenal, ovarian, mesenteric, enteric, omental, and hepatic cysts, hydronephrotic or cystic kidney, perinephritic abscess, Wilms' tumor, splenic tumors, and retroperitoneal tumors and cysts.

Treatment has not been altered radically since Moynihan¹ summarized the possible procedures as: (1) aspiration (Recomier's method), which is not recommended; (2) evacuation and drainage, with marsupialization of the cyst; (3) extirpation, which he did not consider feasible in most instances. Judd⁶ is of the opinion that "the ideal treatment is complete removal, if possible. . . ." He recommended it only for small cysts with few adhesions, but in the same paper cites Bozeman's¹⁸ case, reported in 1881, in which a cyst weighing 20½ pounds

was successfully extirpated. It is generally agreed now that whenever the condition of the patient and the situation and mobility of the cyst are favorable, the cyst safely may be removed en masse. Most of the authorities have recommended aspiration of the cyst prior to extirpation at the time of operation, but in our case the surgeon found it easier to deal with the distended cyst.

If extirpation is performed, the area should be drained, preferably through a separate stab wound. Drainage should cease within ten days or two weeks at most. If a marsupialization operation is performed, the sinus tract may close within about two weeks at best,⁷ or may persist or recur for extended periods of time. Persistent sinus tract may be obliterated by anastomosis with the stomach or small intestine.¹⁰

Prognosis is good if the operation is timely and the postoperative course is uncomplicated. From a prognostic point of view, extirpation probably offers the best outlook, when this method of treatment is possible.

Possible association of a large solitary cyst of the pancreas, such as we have seen, with generalized clinical fibrocystic disease of the pancreas is purely a speculative subject. At last report, two months after operation, our patient was in excellent condition and gaining weight normally, with no intervening illness. It is planned to take samples of duodenal contents later, to determine the presence or absence of pancreatic enzymes.

According to the pathologist's report, this cyst probably should be classified as a pseudocyst of the pancreas. However, the inflammatory changes found in the wall of the cyst may well have been secondary, and the very presence of remnants of pancreatic structure in the cyst wall suggests the possibility that this cyst may have developed as the result of obstruction of one or more ducts, which would place it in the class of retention cyst—a very large one which had outgrown the pancreas, and in which the lining epithelium had been destroyed by pressure of accumulating fluid.

SUMMARY

1. A brief review of the literature reveals seven cases of solitary cyst of the pancreas reported in children, chiefly in infants.
2. A case of a very large solitary cyst of the pancreas is reported in a 6-month-old male infant, in which the cyst was treated by surgical extirpation.
3. An attempt is made to clarify the classification of pancreatic cysts, and diagnosis and surgical treatment methods are discussed, with the recommendation that wherever possible extirpation is the treatment of choice.
4. The possibility of association of some pancreatic cysts with cystic fibrosis of the pancreas is raised for speculation.

The patient was referred by Dr. W. McFadden of Bloomingdale, Mich. Dr. M. Peelen performed the surgery. The pathologic report was furnished by Dr. Hazel Prentice.

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ERYTHEMA MULTIFORME WITH PLURIORIFICIAL LESIONS AND SYSTEMIC MANIFESTATIONS

REPORT OF A CASE WITH RECURRENCE OF MUCOUS MEMBRANE LESIONS

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VON HEBRA¹⁴ in 1866 separated from an ill-defined group of erythemas an entity which he called *erythema exudativum multiforme*. Kaposi⁶ subsequently described a form of the disease in which mucous membranes were involved, and Rendu¹¹ noted cases with fever and constitutional symptoms. Keil,⁷ in reviewing the historical background of the disease, credited Bazin¹ with describing in 1862 the syndrome associated with severe eye complications and stomatitis. In 1922 Stevens and Johnson¹³ reported two cases of "a new eruptive fever associated with stomatitis and ophthalmia." The type of erythema multiforme described by these observers appears to be identical with that earlier reported by Bazin, but the syndrome has come to be known as "Stevens-Johnson's disease." Since their initial report in 1922, approximately seventy other cases have been recorded in the American literature. At the present time, forms of the disease are recognized in which the gastrointestinal and genitourinary tracts, mediastinum, pulmonary system,^{3, 10, 12, 15} and meninges⁸ are also involved.

Erythema multiforme of the type originally described by Bazin and by Stevens and Johnson is characterized by an insidious onset with mild conjunctivitis and stomatitis followed in a day or two by any of the skin eruptions of erythema multiforme. The latter may become vesicular, bullous, or hemorrhagic. Fever and systemic symptoms are usually present in variable degree, depending upon the progression and severity of the skin and mucous membrane lesions. The periorificial areas are swollen and hyperemic, often fissured and hemorrhagic, with crust formation and desquamation. Sometimes anal and vaginal synechiae result. Marked ulceration of the mucous membranes may ensue with sloughing, pseudomembrane formation, and bleeding. Although the oropharynx⁵ and pulmonary system may be involved, the oral and eye lesions are the most striking phenomena encountered.

In mild cases the conjunctival mucous membranes may show only slight erythema, but in severe cases purulent exudate with marked erythema and edema of the lids and even hemorrhage, ulceration, and desquamation may occur. Sloughing of the bulbar and palpebral conjunctivae sometimes follows. The involvement of the eyes may extend beyond the mucous membranes, and panophthalmitis occasionally results. Pseudomembranous formations at times produce keratoconjunctivitis sicca with perforation of the cornea. Chronic conjunctivitis, synechiae, symblepharitis, corneal scarring, and blindness have been observed as sequelae.

The case herein reported was considered to be of interest because of the recurrence of mucous membrane lesions four months after the initial onset. Of additional interest were the investigations pertaining to viral etiology.

CASE REPORT

A 22-month-old female infant was admitted to the Pediatric Department of the Graduate Hospital of the University of Pennsylvania on March 31, 1947.

From the Department of Pediatrics of the Graduate Hospital of the University of Pennsylvania.

because of fever, swelling of the eyelids, blood-streaked saliva, and an urticarial-like skin eruption of two days' duration. On March 18, 1947, the patient had been seen at home by one of us because of rhinorrhea and a dry cough accompanied by slight fever. The mother and brother of the patient had recently recovered from an upper respiratory infection which was epidemic at the time. The patient was treated with a mixture containing codeine phosphate, acetylsalicylic acid, potassium citrate, syrup of ipecac, and syrup of chocolate during the day, and phenobarbital at bedtime. She made an uneventful recovery in a few days. Twelve days after the onset of her illness there suddenly developed a generalized urticarial-like eruption with fever, marked swelling of the eyelids, and swollen, erythematous bleeding gums. Elixir of Benadryl was prescribed. The following day symptoms were accentuated and she was hospitalized.

The patient was born spontaneously at term, weighing 6 pounds, 14 ounces. She was jaundiced for about two weeks following birth and was given small blood transfusions. The mother was Rh negative and the infant, Rh positive. The mother's blood, examined by Dr. Neva M. Abelson during the patient's present admission, showed a low titer of Rh-blocking antibodies. The developmental history of the child was quite normal. She had three attacks of tonsillitis at one year of age and had received the usual immunizations including smallpox vaccination.

Physical examination on admission revealed an acutely ill, well-nourished, irritable infant, with red, edematous, tightly shut eyelids and swollen lips. There was a large hemorrhagic bleb on the lower lip. On the trunk, face, upper extremities, and thighs were scattered and confluent scarlatiniform, morbilliform, and vesicular lesions. Confluent lesions were most prominent on the anterior aspects of the thighs. The palms were involved but not the soles of the feet. When the eyelids were opened with a lid retractor, a clear fluid, under considerable pressure, was found. The corneas were somewhat dulled, and the conjunctivae were congested and edematous. A slough which bled easily covered the oral mucous membranes. The tongue was thick and heavily furred. Saliva mixed with blood and debris drooled constantly. The vagina and anus showed marked hyperemia with sloughing of the mucous membranes and adjacent skin. Superficial lymph nodes were moderately enlarged in the cervical area. A few scattered coarse rhonchi were heard over the lungs. There was no impairment on percussion. The heart was normal in size, and the sounds were of good quality. The spleen was not palpable, but the liver extended about one centimeter below the costal margin on deep inspiration.

On admission, 500 c.c. of 5 per cent glucose in saline was administered intravenously. Penicillin in a dosage of 100,000 units was given intramuscularly every three hours. During the first twenty-four hours she also received 300 c.c. of citrated blood. Nourishment by mouth was impossible during the first seventy-two hours because of the acute oral inflammation. When oral feeding could be instituted, a diet consisting of a mixture of half skimmed milk, ascorbic acid, eggs, vitamin B complex, vitamins A and D, Dextri-Maltose, and casein hydrolysate was given. The conjunctival sacs were flushed with boric acid solution and penicillin (5,000 units per cubic centimeter) instilled alternately every two hours. One drop of one per cent homatropine and penicillin ophthalmic ointment were employed locally in each eye three times daily. Three days later this was changed to $\frac{1}{4}$ per cent scopolamine, one drop daily, and mineral oil instillation alternating with penicillin drops every two hours. The genitalia were flushed several times daily with boric acid solution followed by mineral oil. Petroleum jelly gauze strips were applied to the orificial skin.

A blood count on admission revealed 18,200 leucocytes with 79 per cent neutrophils, 15 per cent lymphocytes, and 6 per cent monocytes. The platelet

count was 489,720 cells per cubic millimeter of blood. A blood culture taken on the day of admission revealed no organisms.

On the third hospital day the cutaneous lesions were typical of erythema multiforme iris. Distributed over the trunk, face, arms, forearms, hands, and the anterior surfaces of the thighs and legs there were vesicles and bullae in the center of large edematous papules. The eyelids were congested, and the left lid was desquamating. The lips were severely hyperemic and showed necrotic areas and bloody debris. The oral mucous membrane appeared to be sloughing, and the tongue was thick and furred. The vagina was swollen, hyperemic, and desquamating. The anus and perianal areas were erythematous and sloughing. The chest revealed mild suprasternal and intercostal retraction on inspiration. The clinical picture was alarming.

The leucocyte count remained within normal limits, and there was no increase in heterophile antibody titer. Cephalin flocculation, thymol turbidity, and colloidal gold tests were within normal limits. Total serum proteins were 6.64, albumin 4.05, and globulin 2.59 Gm. per cent respectively. Total serum cholesterol was 194 mg. per cent, and cholesterol esters measured 142 mg. per cent. Culture from the left eye revealed nonhemolytic streptococcus and from the right eye, hemolytic *Staphylococcus albus*, coagulase negative. Throat and mouth cultures, both by aerobic and anaerobic techniques, yielded *Streptococcus viridans*, *Streptococcus haemolyticus*, and diphtheroids.



Fig. 1.—Fifth day. Eyelids and lips covered with bloody crusts.

The skin lesions on the fifth day appeared dusky red, with hemorrhage in some of the vesicles and bullae. The eyelids were less edematous but continued to be covered with bloody crusts (Fig. 1). The palpebral conjunctivae were covered with a soft, fibrinous membrane, which hung loosely in each eye. Both the bulbar and palpebral conjunctivae had a granular appearance. The leucocyte count was 12,000 cells per cubic millimeter of blood with 75 per cent neutrophils. By the eighth day the child began to take adequate amounts of fluid, in spite of the fact that the lips and mouth continued to bleed. The eyes could be opened, the corneas were clear, and the lids covered with bloody crusts. Many of the skin lesions had begun to dry and crust (Fig. 2). Thereafter, improvement was continuous. The child became less fretful, and the temperature began to fall by lysis. The older skin lesions showed definite signs of involution. Twelve days after admission total serum proteins were 6.48, albumin 3.72, and globulin 2.76 Gm. per cent respectively. Flocculation tests were repeated and found again to be normal.

An intravenous infusion, on the fifteenth hospital day, was followed by two severe paroxysms of chills and a rise in rectal temperature to 106° F. A blood count revealed 42,100 leucocytes per cubic millimeter with 84 per cent neutrophils (promyelocytes 1 per cent, myelocytes 2 per cent, metamyelocytes 10 per cent, band forms 41 per cent, segmented forms 30 per cent), 9 per cent lymphocytes (atypical 4 per cent, typical 5 per cent), and 7 per cent monocytes (atypical 2 per cent, typical 5 per cent). The blood smears showed moderate anisocytosis with tendency to microcytosis and active erythropoiesis as manifested by polychromatophilia and an occasional normoblast. Neutrophilic leucocytosis, with marked toxic granulation and toxic changes in the nuclei of segmented neutrophils, was noted. There was marked left shift with immaturity to the

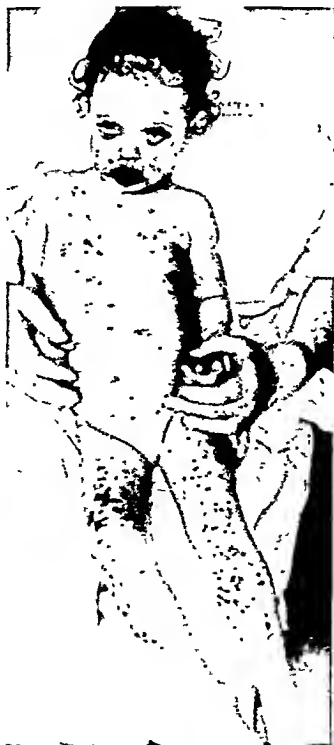


Fig. 2.—Eighth day. Hemorrhagic skin lesions covered with dry crusts.

leucoblasts. Toxic changes were noted in the monocytes and lymphocytes. The platelets were normal in number, appearance, and clumping. The blood picture was considered that of a leucemoid reaction. Streptomycin was started three days later because of the fear of possible secondary infection of the extensive raw surfaces in the mouth, eyelids, and denuded areas on the trunk. Plasma, blood, and glucose in physiologic saline solution were administered parenterally.

Two days later there was less evidence of erythropoiesis, and only an occasional polychromatophilic erythrocyte was noted. Leucocytes were less toxic in appearance with a left shift to the myelocyte stage. Platelets were normal in number, appearance, and clumping. The total white cell count dropped to 27,500 cells per cubic millimeter of blood. Skin lesions had involuted further, but bleeding and crusting of the lips and eyelids persisted.

On the twenty-seventh hospital day the sites of the involuted skin lesions were evident only by residual pinkish yellow macules. The oral mucous membrane was covered with a dirty white slough which bled readily when the child cried. The eyelids continued to show some thin crusts, and there was some whitish yellow, stringy exudate over the palpebral conjunctivae. The corneas were clear and uninvolved. Slight entropion of the left lower lid was evident.

The patient was discharged May 8, 1947, thirty-eight days after admission. At this time the cutaneous and mucous membrane lesions had completely healed. The only sequelae were slight conjunctivitis with minimal entropion of the left lower lid, and photophobia. Pigmented macules persisted at the sites of the former eruptions. Total serum protein concentration on the day of discharge was 7.92 Gm. per cent; serum albumin was 5.64 and globulin 2.28 Gm. per cent. Fasting blood sugar was 96 and blood urea nitrogen 10 mg. per cent. Serologic tests for syphilis were negative, and x-ray studies of the lungs and long bones revealed normal findings. Examination of the spinal fluid disclosed one cell per cubic millimeter, protein concentration of 22 mg. per cent, sugar of 60 mg. per cent, and chlorides of 668 mg. per cent.

Virus studies by the Virus Diagnostic Research Laboratory of the Children's Hospital of Philadelphia was reported by Dr. M. Michael Sigel as follows: "Spinal fluid, bulla fluid, mouth swabs and vaginal swabs collected on April 2, 1947, were examined for the presence of herpes simplex virus and vaccinia virus by inoculation into embryonated hens' eggs and on the rabbit cornea. All tests were negative.

RESULTS OF NEUTRALIZATION TESTS

DATE	INTERVAL AFTER ONSET	VACCINIA	HERPES SIMPLEX
April 24	25 days	1:16	1:64
May 7	38 days	1:256	1:64
July 3	3 months		1:16

"The presence of herpes neutralizing antibodies indicates either present or past infection, but does not establish which, because the first serum was obtained twenty-five days after the onset of illness; however, the failure to isolate herpes virus from numerous specimens taken earlier, strongly suggests that these antibodies were due to a long past infection. The rise in vaccinia-neutralizing antibodies between the twenty-fifth and thirty-eighth days of convalescence could be due to an anamnestic reaction or to a late secondary vaccinia infection of the eroded skin or mucous membrane. Again, the failure to isolate the virus practically eliminates vaccinia as the primary etiological agent."

Two months after discharge the child was active and well. There was a residual mild conjunctivitis and numerous deeply pigmented macules over the site of the former lesions. The entropion had almost completely disappeared.

On July 13, 1947, approximately four months after the onset of the episode which necessitated hospitalization, the child developed a rectal temperature of 101° F., irritability, redness and swelling of the gums and lips. Three days later she was afebrile, and her gums had become slightly hemorrhagic. Two days later the gums, the floor of the mouth, and the labial mucosa were almost completely covered with a gray slough. The eyelids became swollen and thick; yellowish material oozed from the eyes. The skin was not involved. Treatment consisted of hourly swabbing of the mouth with hydrogen peroxide and the instillation of penicillin ointment into the eyes every two hours. Eight days after the onset the gums had healed, the corneas were clear, and the patient was in good condition.

Examination on Oct. 22, 1947 was negative save for slight photophobia and pigmented skin residua.

DISCUSSION

Erythema multiforme with pluriorificial lesions affects males five times as often as females. It occurs most commonly in the spring and fall. Various agents, physical, bacterial, viral, antigen-antibody reactions, and drugs have been incriminated. As yet, no single specific etiological agent has been found. Blood cultures have been reported to be sterile by some authors. Results of eye cultures have been variable. It is likely that bacterial infection when present is due to secondary invasion. Extensive viral investigations,³ employing blood, throat washings, and vesicle fluid in a variety of animals in addition to embryonic hens' eggs, have led to negative results. Histologic studies have been negative for inclusion bodies.

The Commission on Acute Respiratory Diseases³ felt that their studies adequately eliminated as etiological agents the viruses of herpes simplex, vesicular stomatitis, and members of the psittacosis meningopneumonitis group in the material tested. In our case the rise of vaccinia-neutralizing antibodies between twenty-five and thirty-eight days after the onset of symptoms indicates either an anamnestic reaction or a late secondary vaccinia infection of the eroded skin or mucous membranes. The failure to isolate the vaccinia virus can be considered to preclude vaccinia virus as the primary etiological agent. The failure to isolate the herpes simplex virus from specimens taken early in the disease and the presence of herpes-neutralizing antibodies in serum taken twenty-five days after onset of the disease suggest a past infection with herpes simplex virus rather than one concerned with the patient's recent illness.

Drug idiosyncrasies (phenobarbital, nirvaol, Dilantin, phenolphthalein, sulfonamides) have not usually been directly concerned in producing the syndrome. One case resulted when an attempt was made to desensitize a patient who had a strongly positive reaction to an intradermal injection of caseinogen.² It has been claimed to be manifested occasionally after smallpox vaccination.² It is quite possible that the various gradations of erythema multiforme are expressions of antigen-antibody reactions, depending on alterations, both quantitative and qualitative, in tissue or blood protein components. No definitive explanation can be given for the recurrence of mucous membrane lesions.

Studies of blood morphology have not revealed any consistent abnormalities. Anemia when present is probably an expression of the degree of bleeding, the nutritional status of the patient, and the extent of secondary infection. Both leucocytosis and leucopenia have been reported. A leucemoid reaction in our patient, following a sudden rise of temperature with chills and negative blood culture, could be explained on the basis of a pyrogen reaction. Thrombocytopenia has been noted³ and may be related to the purpuric character of the lesions. The platelets were normal in the case herein reported. In another reported case a persistent eosinophilia (15 per cent) was noted.⁴ Various blood chemistry determinations in a small number of reported cases were not abnormal.

Treatment before the advent of sulfonamides and antibiotics was mainly palliative and supportive, being aimed chiefly at maintenance of fluid and electrolyte balance and the prevention of sepsis and other complications. The local and intramuscular use of penicillin and streptomycin and sulfonamides administered orally has greatly simplified the control of infection and sequelae.

CONCLUSION AND SUMMARY

1. A case of erythema multiforme with pluriorificial lesions and recurrence of mucous membrane lesions is herein reported.
2. An etiological agent was sought by cultural methods and viral studies but not found.

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Medical Care

A THERAPEUTIC REGIMEN FOR ACUTE RHEUMATIC HEART DISEASE IN CHILDREN

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THE evaluation of a therapeutic regimen for a protracted illness is one of the most difficult tasks in medicine when the proposed therapeutic program is based upon "unspecific" forms of therapy. Recovery resulting from a form of therapy in such instances may mean complete recovery from the disease, symptomatic relief, or modification of the disease in favor of a more complete recovery. In the case of rheumatic heart disease, for example, recovery may mean complete cessation of rheumatic symptoms, actual interruption of the activity of the disease, or prevention of progressive cardiac damage while rheumatic activity runs its natural course. In proposing such a program it is necessary also to present evidence to show that this therapeutic plan is significantly more effective than no therapy at all or than other forms of therapy given adequate trial. In addition, it is mandatory to show that the particular therapeutic regimen does not produce any untoward effects either in the immediate present or in the distant future.

It is the purpose of this paper to present a therapeutic regimen for acute rheumatic heart disease in children. The forms of therapy proposed are well known; the method and the timing of their application are in some respects new and have been evolved over a ten-year period of intensive experience with rheumatic children observed under adequately controlled conditions.

A large number of rheumatic children (774) 6 to 16 years of age were observed during an episode of acute rheumatic heart disease. The therapeutic program was planned in advance ten years ago and was based upon two generally accepted premises: (1) The duration of rheumatic activity cannot, with our present methods of treatment, be modified, once the disease has passed beyond the stage of invasion. Failure to recognize and adequately treat the disease at the onset of the explosive or exudative phase seems to preclude the possibility of shortening the course of the subclinical or smoldering phase. (2) Acute rheumatic heart disease does not occur in the absence of rheumatic activity; progressive functional disability of the rheumatic heart occurs during rheumatic activity and not during quiescence; and progressive cardiac enlargement is a manifestation of rheumatic activity.

Criteria for the evaluation of the therapeutic results were established and rigidly followed. The type, dosage, and method of application of the thera-

peutic agents were uniformly adhered to and deviations were made only to admit into our program the use of newer forms of therapy as they occurred over the years

During the first five years of this study, the therapeutic program followed closely the commonly suggested forms of therapy (as to dose and method of application) for the various manifestations of acute rheumatic heart disease (1) Salicylates were used when the patient showed obvious manifestations of rheumatic activity. (2) Digitalis was used whenever congestive heart failure manifested itself. (3) Mercupurin was used to increase diuresis when the manifestations of failure were moderate. (4) Oxygen was used only in patients who demonstrated severe respiratory distress*. Little attention was given to dietary regime or fluid intake. In general the patients were receiving a wholesome diet but no restrictions were made in the intake of salt. On the other hand, all of these patients were kept in a good physical and emotional environment. They were all treated in a sanatorium.

During the second five years of this study, a "specific" regimen was adhered to. Definite criteria were established as to when each one of these thera-

TABLE I. FORMS OF THERAPY (SECOND FIVE YEAR PERIOD)

	SALICYLATES	DIGITALIS	MERCURIALS	OXYGEN	DEXTROSE + O INSULIN
	Sodium salicylates	Digitoxin	Mercupurin or mereuhydrim	Chamber B P.—Normal T 66°, CO ₂ 13%	Dextrose—25 50 Oxygen—Cham Insulin—Usua
I	q2h day and night	Single or divided	Single—daily	Continuous	Continuous or rupted
	Oral	Oral	Intramuscular	Respiratory tract	Dextrose—intavenous Insulin subcutaneous
Total	B1 level 35 45 mgm Vol. %	Eeg Digit. effect	1 2 cc.	45 50%	<div> <div>25 gm dextro units insulin Oxygen 45 50 (continuous) Same</div> </div>
e Initial	1½ grains/lb body wt.	1 12 mgm /24 hours	½ 1 cc /day	Same	
Maint	Varies	0 1 0 2 mgm / day	Maint "dry wt"	Same	
ion	6 10 weeks	Varies	End of carditis	End of carditis?	1 Decrease in ity 2 Diuresis (3 6 wks)
Bicarb	Optional				
1 Vit K	1 3 mgm /day				
e1 Vit C	100 300 mgm / day				
Chlorides			Optional 45 60 grs		
n for ruption	Severe salicyl ism (hyper ventilation)	Toxic tachy cardia, ar rhythmas	"Allergy" (vaso motor); dehydration	"Rheumatic Bronchitis"; manifest. failure	Increase in e
Ive result	Laboratory and clinical evidence of carditis subsides	Subjective and objective evidence of failure subsides	Attainment and maintenance of "dry weight"	Laboratory and clinical evidence of carditis subsides	Subjective and objective Evidence of Subsides

* There was no consistent policy established as to when the above-mentioned therapeutic agents were to be interrupted

peutic agents were to be used, how long they were to be continued, and under what conditions they were to be administered. (See Table I.) The therapeutic results obtained in the group of patients treated in the first five years were compared with those obtained during the second five years.

CLASSIFICATION OF ACUTE RHEUMATIC HEART DISEASE

At the very inception of this study, it became obvious that acute rheumatic heart disease cannot be treated as a single entity. It became clear that this phase of rheumatic disease consists of various stages which are distinct in their manifestations and usually follow each other in sequence. It was noted that the disease falls broadly into two main categories: the stage during which the heart is actively disturbed but does not show any evidence of depletion of cardiac reserve; and the phase of obvious congestive heart failure. (See Chart 1.)

MANIFESTATIONS		Cardiac Functional Disability		Congestive Heart Failure			
		Stage of Invasion	Smouldering Phase	Left Heart Failure	Right Heart Failure	Left & Right Heart Failure	"Irreversible" Heart Failure
Toxic	Fever, Pallor	▲	Δ				▲
	Weakness, Cold and Clammy Skin	▲					▲
	Anorexia, Vomiting	▲					▲
	Anxiety, Restlessness	▲		Δ		Δ	▲
	Other Rheum. Manif. - Muscle, Joint, Skin	▲	Δ				Δ
Cardio-vascular	Heart Rate - (Tachycardia)	▲	▲	Δ	Δ	Δ	▲
	Fatigability	Δ	▲	▲	Δ	Δ	▲
	Angina		Δ	▲		▲	▲
	Dyspnoea and/or Orthopnoea			▲		▲	▲
	Abdominal and GI Symptoms				▲	Δ	▲
	Dependent Edema				▲	▲	▲
	Labile Pulse	Δ	▲	▲	Δ	▲	▲
	Rhythm Disturbance (crude)	Δ		Δ	Δ	Δ	▲
	Blood Pressure	Decrease	Rise	No change	No change	No change	Rise
	Vital Capacity (decrease)		2+	4+	1+	2+	4+
	Ventilation (increase)		1+	4+	1+	2+	4+
	Venous Pressure (increase)				4+	2+	4+
	Circulation Time (increase)		2+	1+	2+	2+	4+
	Cardiac Enlargement		1+	1+	2+	2+	4+
Laboratory	Elevated ESR, increased WBC, Depressed RBC and Hb	▲	Δ	Δ			
ECG	Conduction Disturbance A-V	▲	Δ				Δ
	Prolonged QTc	▲	▲	▲	▲	▲	▲
	Local Tissue Anoxia - ST	Δ	▲				Δ
	Myocardial Disturbance - T			▲	▲	▲	▲
	Ventricular Strain - Left or Right					▲	▲
	Disturbance in Rhythm						▲

▲ Usual
Δ Occasional
1+ Slight
2+ Moderate
4+ Marked

Chart 1.—This chart shows the usual manifestations observed in most of the cases during each one of the phases of acute rheumatic heart disease.

I. CARDIAC FUNCTIONAL DISTURBANCE

Most patients at the onset of acute rheumatic heart disease show unequivocal evidence of cardiac disturbance without signs or symptoms of congestive failure. A marked tachycardia, easy fatigability, slight dyspnea on exertion, changing heart sounds and murmurs, and electrocardiographic alterations are observed much in advance of the classical signs of congestive heart failure. This

phase of the disease known as carditis is the most common single manifestation of rheumatic disease in children and may have a duration of three months to several years. It may be acute or smoldering. The degree of carditis may fluctuate from minimal to severe, leading rapidly to the second phase, namely, congestive heart failure.

A. The Stage of Invasion.—At the onset of carditis, the acute phase is dominated by the usual toxic manifestations of rheumatic fever. The patient has fever, is extremely pale, complains of weakness, marked perspiration, and cold and clammy skin. There is a high degree of emotional disturbance such as anxiety, restlessness, capricious appetite, irritability, etc. The child is likely to show other rheumatic manifestations in this phase of the disease. He usually presents arthritic manifestations, various skin manifestations such as erythema marginatum, etc. The usual laboratory tests such as the erythrocyte sedimentation rate, white blood count, hemoglobin determination—tests which are thought to be contributory to the diagnosis of rheumatic fever—are in most instances found to be positive in this stage of the disease.

On the cardiovascular side, there are few obvious findings. The child has a tachycardia; complains occasionally of fatigability; and has a slight decline in systolic pressure. There is no change in the circulation time and no increase in venous pressure. The heart does not show progressive cardiac enlargement on repeated examinations. On the other hand, nine out of every ten patients show a disturbance in conduction time on the electrocardiogram and all patients in this group show a very definite prolongation of the systolic time on the electrocardiogram.

While, therefore, the stage of invasion presents the usual "classical" manifestations of rheumatic fever, there is at the same time clear clinical and electrocardiographic evidence of mild cardiac disturbance.

B. The Smoldering Phase.—Once the acute toxic phase is passed, the patient settles down to a long drawn out, usually low-grade carditis. During this period very few of the toxic manifestations are present. The child usually has a normal temperature. The pallor is greater than the hemoglobin would warrant but is not as intense as in the stage of invasion. The diagnosis is often uncertain since the usual laboratory tests may be completely normal and may continue to be normal for many months while the activity of the disease continues. On the other hand, more definite manifestations of cardiac functional disability begin to accrue. The heart presents a tumultuous cardiac rhythm with a sinus tachycardia. The child occasionally complains of anginal pain and easy fatigability. On examination, the pulse rate is found to be labile. The blood pressure is usually higher than would be expected for the age of the child. There is a moderate decrease in vital capacity and an increase in respiratory rate as well as in ventilation. Repeated roentgen examinations show progressive cardiac enlargement. The electrocardiogram always shows a marked disturbance in the relationship between electrical systole and diastole. As has been pointed out elsewhere,¹ the Q-T interval is always markedly prolonged. The diastolic period is, therefore, very much shortened. The heart works under a false economy

of a prolonged contraction time impaired by a markedly shortened relaxation time. In most instances, when this sequence of events continues unabated, the electrocardiogram begins to show signs of local tissue anoxia. There are, however, no obvious signs of depletion of the cardiac reserve. There is no dyspnea or orthopnea. The venous pressure is normal and the blood velocity is within normal limits.

It would seem, therefore, that during the smoldering phase of carditis, the patient shows some adaptation to the disease process. He no longer shows clinically the toxic effects of the disease. On the other hand, he shows very definite disturbance in cardiac function as measured by some cardiac symptoms and evidence of disturbance in the integrity of the heart muscle on the electrocardiogram. There are no obvious signs of failure.

This phase of the disease may go on for months without entering the phase of failure. The greatest majority of patients do not show failure until a much later stage. A large number of these patients do not escape cardiac failure unless appropriate therapy is carried out.

II. CONGESTIVE HEART FAILURE

The average child with rheumatic heart disease does not show congestive failure unless a long period of carditis has preceded. This, of course, excludes the few rare occasions of a fulminating type of pancarditis. It has been observed that in children the earliest manifestation of heart failure concerns the left side.

1. Left Heart Failure.—At this stage, many symptoms of cardiac involvement manifest themselves. There is easy fatigability. There are frequent attacks of angina. There are various degrees of dyspnea or orthopnea. Upon examination, while the toxic manifestations of rheumatic fever are not prominent, there are undoubted signs of acute carditis present. The pulse rate is labile. There are occasional disturbances in rhythm, and from time to time a distinct gallop rhythm is heard. There is usually a marked decrease in the vital capacity and the ventilation is markedly increased. The blood circulation time is occasionally prolonged, although the venous pressure in most instances is normal. The heart is always found to be enlarged. The electrocardiogram shows the ever present disturbance in the systolic-diastolic relationship as well as distinct evidence of myocardial disturbance. T-wave changes in the limb as well as in the precordial leads are a frequent finding.

The degree of left heart failure may vary from that of minimal signs of respiratory distress to frank pulmonary edema and this may occur in the absence of any obvious signs of right heart failure.

2. Right Heart Failure.—Pure right heart failure is rarely seen in rheumatic heart disease in children. When it does occur, it is rather striking in that the child shows an enlarged liver, edema, and occasionally, facial edema without any signs of respiratory distress. The majority of patients do not demonstrate any toxic manifestations of rheumatic disease. The laboratory tests are usually normal for acute infection but many signs and symptoms of cardiac

failure are present. In this phase, the gastrointestinal symptoms are more likely to dominate the scene. There is nausea, vomiting, disturbances in evacuation, frequent upper abdominal pain, and distention.

The pulse rate is found to be labile. The blood pressure is normal and there is only a slight increase in ventilation. The vital capacity may be decreased only slightly. The venous pressure is raised and the blood circulation time is delayed. The heart is moderately enlarged. The electrocardiogram shows the usual disturbance of the relationship of systole to diastole and evidence of myocardial damage particularly as manifested by changes in the T wave.

In our experience, when right heart failure remains unabated for some time, the next phase of cardiac failure is inevitable.

3. *Left and Right Heart Failure.*—At this stage there are few manifestations of the toxic rheumatic disease. There are, frequently, complaints of precordial pain often typically anginal in character. At other times, the precordial distress is of an indefinite nature; diffuse precordial annoyance and a feeling of constriction. The patient shows the manifestations of respiratory distress as well as the manifestations of right heart failure. There is dyspnea and orthopnea. There are occasional gastrointestinal symptoms. The venous pressure is raised and the circulation time is delayed. The vital capacity is low and the ventilation is high. The heart becomes markedly enlarged. At this stage, the usual electrocardiographic findings are those of ventricular strain either right or left. In addition, the patient continues to show clinical evidence of carditis. The pulse is labile, the heart is tumultuous, and there is frequently a marked gallop rhythm. There are occasional crude disturbances in rhythm in addition to a marked tachycardia.

Many of these conditions, as will be shown later, are reparable and the patients return to a relatively good state of cardiac reserve. Some progress to the "irreversible" stage.

4. *"Irreversible" Stage.*—At this phase, there is a distinct and rather dramatic return of all the toxic manifestations of rheumatic disease. There is low-grade, fluctuating fever and marked pallor. The patient once again complains of extreme weakness, cold sweats, and a cold, clammy skin, and shows marked anxiety and restlessness. There is a recrudescence of joint swellings with many bizarre rheumatic skin manifestations, a marked tachycardia, and extreme cardiac fatigue. The patient often has acute attacks of angina. Some of these attacks are long lasting and difficult to control with sedation. There is marked dyspnea and orthopnea. The liver is markedly enlarged. The upper abdomen is tender, and there is usually a high degree of edema and ascites. Most patients in this stage show a considerable rise in systolic blood pressure; a marked rise in venous pressure and a great delay in circulation time; a marked depression in vital capacity and a marked increase in ventilation sometimes reaching as much as ten liters per minute per square meter of body surface. The heart is markedly enlarged. The electrocardiogram in this stage may show any or all of the abnormalities mentioned previously. Many patients also show crude disturbance in rhythm such as auricular fibrillation, premature

ventricular contractions, etc. All patients show a marked prolongation of the systolic period on the electrocardiogram and a relatively marked shortening of the diastolic period.

It is noteworthy that in spite of the high degree of failure, many cases show positive laboratory evidence of active infection such as an elevated erythrocyte sedimentation rate, an elevated white blood count, and a marked depression in the hemoglobin.

In summary, it might be said that there are six distinct stages in the evolution of acute rheumatic heart disease leading to "irreversible" failure. The first is the stage of invasion where the picture is dominated by the toxic manifestations of acute rheumatic fever. Few if any symptoms of heart disease are present and the earliest inkling that the heart is involved is expressed in disturbances in conduction time on the electrocardiogram. The next four stages no longer demonstrate the toxic manifestations of rheumatic disease but show more evidence of cardiac disability as the disease progresses from the smoldering phase to the phase of left and right heart failure. And finally, there is the "irreversible" stage of heart failure where the degree of activity of the disease is once again at a high level and the degree of severity of heart failure is markedly increased.

It may be noted that the only feature which is present in all these phases and which in our opinion demonstrates the presence of active carditis is the disturbance in the systolic-diastolic relationship of the cardiac function: systole is prolonged and diastole markedly shortened.

THERAPEUTIC MEASURES (CHART 2)

In the planning of any therapeutic regimen, it is customary to consider the following therapeutic measures:

- A. The external environment under which the patient is being treated.
- B. The internal environment which is provided for him in terms of nutrition.
- C. The specific or supportive medication.

A. The Environment Under Which the Patient Is Being Treated.—It has long been recognized that for a patient suffering from heart disease, complete rest is needed first and foremost. In recent years more stress has been placed upon emotional rest rather than physical rest. In some quarters, the pendulum is swinging away from restricted bed rest to avoid complications which are inherent in prolonged rest.²

Experience with acute rheumatic heart disease teaches two lessons in this respect: (1) Physical rest continues to be a most essential part of the treatment as long as rheumatic activity in the heart muscle is present. Failure to attain a good measure of physical rest interferes with all other forms of therapy. Experience has also shown that an increase in physical activity during the phase of active rheumatic disease encourages progressive cardiac damage during that phase of the disease. It has become perfectly obvious that unless an

environment is created whereby the child has complete emotional rest in the form of security and a certain measure of contentment and happiness, the necessary degree of cardiac rest cannot be attained. It is for this reason that sanatorium care³ is suggested. It is also for this reason, in our opinion, that results attained at the sanatorium compare most favorably with results attained elsewhere.

THERAPY		Cardiac Functional Disability		Congestive Heart Failure			
		Stage of Invasion	Smouldering Phase	Left Heart Failure	Right Heart Failure	Left & Right Heart Failure	"Irreversible" Heart Failure
Cardiac Rest (Physical and Emotional)		+	+	+	+	+	+
Dietary Regimen	High Protein	+	+	+	+		
	High Vitamin	+	+	+	+	+	+
	Na Poor			+	+		
	Na Free					+	+
	Cl Increase			+	+	+	+
	Fluid (amt)	normal	normal	increased	increased	2-3 qts/day	Limited
"Specific" Medication	Salicylates	●	□	□	□	□	□
	Digitalis	*	*	*	○	?	*
	Mercurials	?	?	●	○	●	●
	Digitalis + Merc.	*	*	*	●	○	□
	Oxygen	○	●	?	□	?	□
	Dext + O ₂ + Insulin	?	□	□	?	?	●

● Most Effective
○ Effective
? Questionable Value

□ Ineffective
* Contraindicated
+ Indicated

Chart 2.—This chart shows the therapeutic regimen that was followed during the second five-year period.

B. Nutritional Requirements.—The influence of diet upon the progress of rheumatic heart disease has been discussed for many years. The pendulum has swung from limited Karrel type of diets to high calorie, high protein, high vitamin diets. Our experience shows that during the stage of invasion and the phase of protracted carditis as well as early cardiac failure, a high protein high vitamin diet seems to produce more favorable results than diets poor in sodium and limited in calories. When the patient has reached the stage of both left and right heart failure, it would seem that the best results are attained by putting the patient on a sodium poor diet in the form of a modified Karrel diet. The routine has been to place the patient on one to one and one-half quarts of milk daily or about 1 to 3 Gm. of sodium daily. When the patient has reached the "irreversible" phase, this diet becomes mandatory if any results are to be attained.

The fluid intake during the first two phases of acute rheumatic heart disease need not be modified. Once the cardiac reserve is impaired, it would seem that the fluid intake must be increased, and when the patient has reached the phase when he has both left and right heart failure, a regimented effort must be

made to increase the fluid intake to between two and three quarts daily. This increase in fluid, however, cannot be continued once the patient has entered the "irreversible" phase. At this phase the fluid intake must be sharply limited. The reason for this is not at all clear.

To summarize, our nutritional regimen is predicated upon the following principles: (1) During the stages of invasion and functional cardiac disability when the cardiac reserve presumably is normal, the patient should be kept on a high protein, high vitamin diet with a normal amount of fluid and salt intake; (2) Once the patient enters the phase of decrease in cardiac reserve, a modification of the diet is an important part of the program depending upon the degree of decrease in cardiac reserve. The more the cardiac reserve is depleted as expressed by the degree of cardiac failure, the more limited does the diet have to be principally for the purpose of decreasing the salt intake, and the larger does the fluid intake have to be to attain satisfactory diuresis. The exceptions to this rule are the patients in whom the cardiac reserve is very low and the element of rheumatic activity high. In these instances, the patient does not seem to be able to excrete the sodium but at the same time cannot tolerate even a normal amount of fluid intake.

C. "*Specific*" or *Supportive Medication*.—In the treatment of acute rheumatic heart disease many forms of therapy have been used. Salicylates, digitalis, mercurials, oxygen, concentrated glucose, all have been used from time to time. The reported results with these various forms of therapy range from complete disappointment to a high degree of enthusiasm. From our point of view, the reason for such a discrepancy in reported results is not the form of therapy but the choice of patients to whom it was administered.

1. *Salicylates*: In our experience, salicylates in large doses may be considered in the nature of a specific therapy if given to the patient during the stage of invasion. Thus, when a patient suffers from an acute carditis in the exudative stage, particularly during the first six weeks after the onset, large doses of salicylates more often than not (80 per cent of the cases) interrupt the onslaught of the illness. All clinical and laboratory evidence of activity subsides and the patient makes a complete recovery, often within a period of a few weeks. The results in these cases are not unlike those seen in instances of acute polyarthritis. Our experience teaches that eight out of every ten patients, if treated at this time with sufficient salicylates to raise the salicylate level to between 350 and 450 micrograms, can be saved from the next phase of the disease, namely, the smoldering type of carditis.

In addition, there is solid evidence to show that salicylates in sufficient dosage make no impression upon the course and the outcome of acute rheumatic heart disease if they are administered after the stage of invasion. Briefly, therefore, proper salicylate therapy is an important form of treatment if applied at the proper phase of the disease.

2. *Digitalis*: It has repeatedly been stated that the so-called "specific" drug for heart disease has been losing ground in its importance particularly in the treatment of acute rheumatic heart disease.^{4a, b, c, 5, 6, 7} For many years we have

been impressed with the fact that the ill effects of the proper use of digitalis in acute rheumatic heart disease outweigh any possible beneficial effects. In our experience, there is no stage in the disease where digitalis alone can be said to be most effective. On the other hand, there are many stages in the disease during which the use of digitalis produces incontrovertible evidence that more harm is done by the use of the drug than by withholding it. It is generally agreed that patients with acute hearts may be more sensitive to the usual doses of digitalis. On this account, a careful plan has been followed in the use of digitalis in acute rheumatic heart disease. In all cases concentrated digitalis preparations are used controlled by repeated cardiographic tracings to gauge full dosage as well as toxic effects. Enough evidence has accrued to show that during the stage of invasion and the stage that follows, namely, the stage of functional disability of the heart, as well as during the stages of left heart failure and so-called "irreversible" heart failure, proper use of digitalis produces toxic effects much before any therapeutic effects are observed. In many cases these toxic effects with doses too small to expect any therapeutic effects range from premature contractions to toxic rhythms, and all types of arrhythmias. Occasionally, in instances of right heart failure digitalis seems to be effective when used alone.

Briefly, the use of digitalis in acute rheumatic heart disease is of limited value. In our experience, it would seem that one might well do without the use of this drug in the vast majority of instances. The possible exception to the rule would be in auricular fibrillation with a fast ventricular rate. Even in these cases when the arrhythmia occurs during the so-called "irreversible" phase or during the phase of "pure" left heart failure, the usual effect of digitalization upon auricular fibrillation is not attained in the average case.

3. Mercurials: Our experience coincides with the experience of other observers that when mercurials are properly used, they take the place of digitalis in acute heart disease. During the first two phases of acute heart disease it is of questionable value. The patients showing symptoms of left heart failure can be treated most effectively with the use of mercurials. Frequent small doses given intramuscularly must be continued until dry weight is attained and from then on the patient is placed on a maintenance dose of Mereupurin or Mereuhydrin until all evidence of acute heart disease has subsided. It is important to remember that mercurials are continued not only until evidence of congestive failure has subsided, but until all evidence of rheumatic activity is no longer present. This form of therapy may have to be continued for many months.

There are no contraindications to the use of mercurials if they are used judiciously. It is widely agreed that mercurials should be used intramuscularly rather than intravenously as the occasional fatality that occurs as a result of mercurial injection is limited to the patients who received the medication intravenously. Furthermore, the effect in our group of patients can be produced equally well with the intramuscular route. Occasionally (1 in 200 patients) a child will show what seems to be an allergic response to a certain form of

mercurial diuretic. This allergic response is expressed usually in the form of a vasomotor collapse ranging in severity from mild and transitory to severe, necessitating emergency cardiac therapy. When such response occurs with Mereupurin, Mereuhydrin does not produce the same response, and vice versa. The nature of this sensitivity is not clear. Some children develop signs of severe dehydration but this can be avoided by giving ample amounts of fluids during the course of the mercurial therapy.

4. *Oxygen Therapy*: The routine use of oxygen therapy in acute heart disease has not been proposed definitely heretofore. The method which we employ and the results which we attain thereby have been described elsewhere.⁸ The routine is as follows: The patient is placed in an oxygen chamber containing 45 to 50 per cent oxygen and 1 to 1.5 per cent carbon dioxide. He is kept in the chamber until all clinical and laboratory evidence of carditis have subsided. The duration of this period may range from ten weeks to several months.

We have observed no beneficial effects from oxygen in cases of acute heart disease with heart failure. Furthermore, in the irreversible type of heart failure, oxygen therapy alone is definitely ineffective. In cases of left heart failure, it is of questionable value. This form of therapy, however, is of specific value in the smoldering type of carditis which demonstrates no depletion of cardiac reserve but shows all the evidence of impairment in the functional integrity of the heart. In these instances, the effect is striking and rapid. An analytic description of the value of this form of therapy for these cases has been presented elsewhere.⁸ In our experience there are two definite contraindications to oxygen therapy in acute rheumatic heart disease in children. Patients who present evidence of bronchitis during the course of rheumatic activity should not be introduced into a high oxygen atmosphere. All of these patients develop severe symptoms of respiratory distress and must be removed almost immediately. The mechanism of this is not clear. The group of patients, as mentioned above, who manifest advanced heart failure do poorly in a high oxygen atmosphere.

5. *Concentrated Glucose*: The use of concentrated glucose in heart disease has been tried from time to time. In our experience, the cases of so-called "irreversible" heart failure where the toxic element of the disease is high and at the same time the cardiac reserve is extremely low, a few cases are definitely improved by the use of this form of therapy.

The patient is given intramuscularly 25 Gm. of dextrose daily. This is given in two doses, of either 25 c.c. of a 50 per cent solution or 50 c.c. of a 25 per cent solution, one dose before breakfast and the second dose in the early evening. At the same time, the patient receives subcutaneously an injection of insulin equivalent to about one unit to every three or four grams of carbohydrate. In addition, the patient is given oxygen for one hour by mask or catheter following the injection of dextrose. This form of treatment is continued until all signs of toxicity subside and a well-established diuresis has been attained. The average patient needs approximately three to six weeks of this form of therapy. Once the patient shows the above-mentioned signs of improvement and is no longer considered as having the "irreversible" type of

heart failure, he is then treated with mercurials used in the method described above. The effectiveness of this type of therapy in the "irreversible" group of cases is questionable since only about one in ten patients seems to be relieved. In our experience, a great many patients early in the course of the treatment show failure to respond. The only contraindication to this form of therapy that we have observed is increasing dependent edema which seems to be definitely associated with the therapy rather than the course of the disease.

In summary, therefore, it may be said that while the types of medication administered in this regimen have been used from time to time, the method of application is new. Salicylates are an almost specific form of therapy when used during the stage of invasion. Oxygen therapy seems to belong in the same category if used in the stage of smoldering carditis without heart failure. Mercurial diuretics used in a specific way have displaced the use of digitalis in acute left heart failure. Digitalis finds limited use in acute rheumatic heart disease but may be tried in cases where the dominant feature is right heart failure. In the patients in whom the activity of rheumatic disease has depleted the cardiac reserve as manifested by both left and right failure, the use of mercurials in addition to digitalis seems to be the therapy of choice. The proposal to use concentrated glucose with oxygen and insulin is made with misgivings. It seems that a few of the so-called "irreversible" heart failure patients do well with this form of therapy.

RESULTS

In the past five years (1942-1947), 376 children with acute rheumatic heart disease were treated in the manner described above. These were carefully classified first as to the phase of acute rheumatic heart disease. They were then placed on the appropriate treatment as outlined. In the preceding five-year period (1937-1942) another group of 398 patients were also classified as to the phase of the disease that they presented but the treatment in this group was not systematic and did not follow any particular pattern. In most cases of the latter group, salicylates were used in all phases of the disease where a diagnosis of active rheumatic disease was made. The dose was insufficient in most cases and no attempt was made to gage the dose by determining the level of the salicylates in the blood; digitalis was used liberally; mercurials were used where evidence of heart failure was present but this was used in interrupted doses and results were judged by the amount of diuresis attained at the time. No attempt was made to determine a maintenance dose, and mercurial diuretics were stopped as soon as obvious evidence of failure subsided. Oxygen was used only as an emergency form of therapy. Patients were treated in oxygen tents or by catheter when severe signs of heart failure were present, particularly left heart failure. The use of glucose, oxygen, and insulin was attempted only as a form of emergency cardiac therapy.

When the two groups are compared, i.e., the group treated during the first five-year period and the group treated in the last five-year period, striking differences are observed. (See Chart 3, Table II.) Of the total number of 398

mercurial diuretic. This allergic response is expressed usually in the form of a vasomotor collapse ranging in severity from mild and transitory to severe, necessitating emergency cardiac therapy. When such response occurs with Mercupurin, Merehydrin does not produce the same response, and vice versa. The nature of this sensitivity is not clear. Some children develop signs of severe dehydration but this can be avoided by giving ample amounts of fluids during the course of the mercurial therapy.

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phases of acute heart disease. In the stage of invasion and in the smoldering phase, eight out of every ten patients recover from the acute attack if given the proposed form of therapy, whereas formerly the recovery rate was from 30 to 46 per cent. Of the patients who show a depletion of cardiac reserve, the recovery rate is more than twice as great with the present form of therapy as with that used in the past. In the group with left heart failure, three out of every four patients recovered from the acute attack; of those with right-sided failure, three out of every five; in those with both left and right failure, one out of every two; and in the "irreversible" group, one out of every ten. The best results during the first five-year period were three out of every ten patients in any phase of congestive failure and in the "irreversible" group, none recovered.*

Of those children who did not recover in either of the two groups, some became progressively worse, graduating from a milder phase of acute heart disease to a more severe phase, and some died during the acute attack. Almost one-half of the patients treated in the first five-year period became progressively worse and practically one-third of the patients died during the acute attack. With the newer therapeutic regimen, only 22 per cent became progressively worse and a total of 11.1 per cent died during the acute attack. These results become more striking when one subdivides them according to the various phases of acute heart disease. In the stage of invasion, if the patient is treated inadequately, his chances of becoming progressively worse are about 60 per cent as compared with 10 per cent when treated adequately. In the smoldering phase, one out of every two patients becomes progressively worse with the old system of therapy as compared with one in every four when treated with the new regimen. In the group of patients with heart failure, one out of every two becomes progressively worse when inadequately treated, but when therapy is adequate, of the patients with left heart failure only one in six might become progressively worse and in right heart failure and in left and right heart failure from one-quarter to one-third of the patients become progressively worse.

In all the phases of acute heart disease, the mortality rate is much lower in the group which is adequately treated as compared with the group which is treated in the old manner. It is obvious that the mortality rate rises in both groups as the disease progresses from the early stage of invasion to the "irreversible" phase. But the mortality rate is significantly lower during the second five years of this study.

COMMENT

There is general agreement that the interest in the treatment of rheumatic fever and rheumatic heart disease has lagged behind when compared with the ever-increasing interest in the etiology and pathogenesis of this disease. The reason for this lag stems from the fact that the clinical concepts relative to the course and behavior of acute rheumatic disease have for many years been nebulous and confusing. Thus a therapeutic hopelessness has dominated the thinking as regards the treatment of this disease.

*That is where the name "irreversible" found its origin.

patients treated in the first five-year period, about 25 per cent made a recovery from the attack for which they were treated. In the group of patients treated in the last five years, the recovery rate was more than twice as high (58.7 per cent). This difference becomes even more striking as we analyze the various

Comparison of Past and Present Methods of Therapy

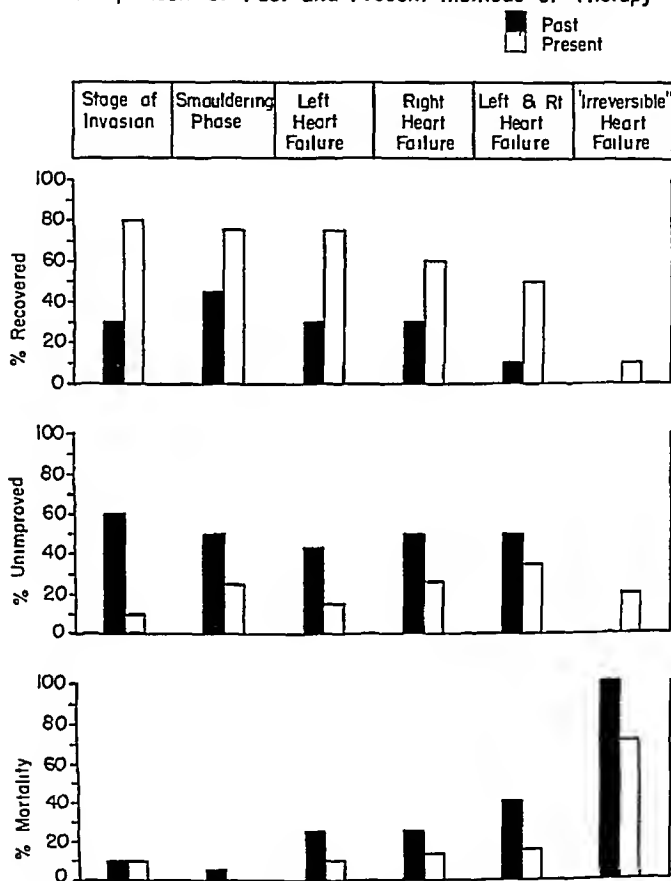


Chart 3—This chart shows the percentage incidence of patients recovered, unimproved, and the mortality in each of the two five-year periods

TABLE II. COMPARISON OF PAST AND PRESENT METHODS OF THERAPY

	NUMBER OF PATIENTS		RESULTS					
			% RECOVERED		% UNIMPROVED		% MORTALITY	
	PAST	PRESENT	PAST	PRESENT	PAST	PRESENT	PAST	PRESENT
Stage of invasion	60	50	30	80	60	10	10	10
Smoldering phase	50	40	46	75	50	25	4	0
Left heart failure	68	60	31	75	45	15	24	10
Right heart failure	100	130	30	60	50	27	20	13
Left and right heart failure	80	66	10	50	50	35	40	15
"Irreversible" failure	40	30	0	10	—	20	100	70
Totals	398	376	25.1	58.7	45.7	22.7	29.1	11.1

The methods of application and timing of the therapeutic measures discussed in this paper have been evolved in an environment which played an important role in producing the results noted above. It must be said that without the complete physical and emotional rest such as can be attained only in a sanatorium type of environment, the therapeutic effects would fall short in producing the favorable results presented. On the other hand, sanatorium environment alone without a systematic therapeutic regimen fails to effect the clinical course of the disease in a significant way. The primary aim in the treatment of acute rheumatic heart disease is the attainment of complete cardiac rest during the unfavorable circumstances imposed upon the heart by the presence of an acute inflammatory process in the heart muscle. Thus, when the period of invasion has proceeded unchecked, complete cardiac rest can be attained by relieving local tissue anoxia or by decreasing the burden imposed upon the heart by those dynamic factors which are responsible for cardiac failure.

CONCLUSIONS

1. A therapeutic regimen for the treatment of acute rheumatic heart disease in children is presented.
2. Acute rheumatic heart disease has been classified into six phases.
3. The stage of invasion can be treated most effectively with adequate salicylate therapy.
4. The stage of protracted carditis can be favorably influenced by adequate oxygen therapy.
5. The stage of heart failure is adequately treated with dehydration therapy attained by a regimented use of mercurials and salt and fluid intake.
6. Complete physical and emotional rest, best attained in a sanatorium type of environment, plays an important role in the proposed therapeutic program.

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In recent years, it has become fairly clear that disability resulting from rheumatic heart disease is an expression of the acute inflammatory process in the heart muscle rather than the extent of valvular damage. This concept implies that the chemical or metabolic changes which take place during the acute phase of the disease contribute much more to the functional disability of the heart than does the mechanical impairment of the heart as a pump resulting from fibrosis of the valves. If, then, we adhere to this concept, it is obvious that the treatment of rheumatic heart disease during the acute phase is the primary aim in the management of the cardiac disability resulting from rheumatic disease. Our experience in this regard teaches the important lesson that the outlook for the patient with acute rheumatic heart disease is not hopeless but favorable indeed provided that the therapy is aimed at: (1) stopping the invasion of the heart muscle at the onset of rheumatic carditis; (2) relieving myocardial anoxia before heart failure has become manifest, and; (3) improving impaired cardiac function by relieving the signs of failure occurring during the acute phase of the disease.

We are impressed from the experience presented in this paper that a judicious, fearless, and patient use of salicylates distinctly delimits the invasion of the disease. Once the invasion has advanced unhindered, the duration of rheumatic activity cannot be shortened. At this stage of the disease, relieving the burden imposed upon the heart muscle by local tissue anoxia prevents, in a large majority of cases, cardiac disability as expressed in congestive heart failure. The treatment of these two phases of the disease, therefore, is of paramount importance and if carried out properly decreases the total cardiac damage resulting from rheumatic disease. Once the heart has begun to fail, dehydration therapy must be given to prevent further failure. This dehydration therapy can best be attained by adequate control of salt and fluid intake and by persistent and judicious use of mercurial diuretics.

It has been mentioned from time to time that digitalis therapy in acute rheumatic heart disease is of limited value. Our experience concurs with this observation. We are, on the other hand, impressed with the fact that digitalis in proper therapeutic dosage in acute rheumatic heart disease cases produces toxic digitalis effects much before any therapeutic effects may be obtained. It would seem that the patient with acute rheumatic heart disease shows a high degree of sensitivity to digitalis precluding its use to produce therapeutic effects. It is further clear that the more acute the carditis, the more precarious is the use of digitalis. We have not been convinced that the toxic effects of digitalis produced in acute rheumatic heart disease are a matter of improper dosage.

It is common experience that under the best of therapeutic conditions, many patients with acute rheumatic heart disease go downhill toward a catastrophic end. This group of patients, in our experience, seems to manifest an acute explosive recrudescence of rheumatic disease superimposed upon a heart whose reserve has already been markedly depleted. It would seem from the experience presented here that an attempt to improve cardiac nutrition may yet save a few of these individuals.

of the promises she had made as best she can. The child then feels that he has been betrayed and let down by someone on whom he should be able to rely; he is likely to look on his admission to the hospital as an abandonment by his parents. Some hospitals do not permit the parent to accompany the child to the ward, thereby increasing the feeling in the child that he has been left by those who should love him. If the physician on the ward is not the one who sees the child in the clinic, the child feels that no one in the hospital is familiar with him or his problems. In practice, when the mother is permitted to accompany the child to the ward and to talk to the nurse who will later have charge, the degree of separation anxiety in the child is lessened and his adjustment to ward routines is enhanced. The wise physician will try to ascertain what the child has been told of the reasons for coming to visit the doctor or for admission to the hospital.

Children are often exceedingly poorly prepared for routine visits to the physician and may be told fantastic tales as to why they are going to be admitted to the hospital. One boy with acute appendicitis was brought to the hospital in the middle of the night in his pajamas with his sled, having been told by the parents that he was going for a sleigh ride. It was several days before he could meet any of the hospital personnel without an attitude of complete suspicion. Another boy who had been told by his father that he was to have an enema and then go home, awoke from the Avertin anesthesia with a surgical dressing on his abdomen and refused to talk to his father during the rest of his stay in the hospital after greeting him initially with the remark, "Daddy, you are a liar."

If visiting hours are restricted it should be made clear to the child that the decision is one made for, not by, the parent. Parental visiting is often an upsetting event for the child and is regarded as necessary but bothersome by the hospital personnel. Troublesome parents may be discouraged from visiting; this procedure does not take into account the child's bewilderment as to why other parents visit but his do not.

ILLNESS AS PUNISHMENT

Although the meaning of a specific illness to a particular child depends upon a large number of factors in his past experience and on the attitudes of his parents, there are some things which are common to most children who become sick and which affect their attitudes and reactions toward the illness. To most children sickness comes as punishment for their misdeeds. In this belief children differ little from our ancestors only a few generations ago when sickness was regarded as punishment for the collective and individual sins of mankind. Beverly¹ reported in 1936 that 90 per cent of a group of children at the Children's Memorial Hospital in Chicago stated that they got sick because they were "bad"; eighteen out of twenty-one diabetic children said that they "ate too much sugar"; and 90 per cent of a cardiac group believed that they were ill because they "ran too much."

Similar ideas were garnered from children who were patients in the Babies Hospital. Almost all of the children seen a few years ago in a convalescent home for children with rheumatic heart disease subscribed to the belief that their illness was, at least in part, caused by disobedience of parental commands and

Psychologic Aspects of Pediatrics

PHYSICAL ILLNESS AND CONVALESCENCE: THEIR MEANING TO THE CHILD

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IT IS the rare child who grows into maturity without having gone through one or more episodes of physical illness. Clinical psychiatric observations reveal that physical illness in a child, no matter how trivial, has its own unique meaning for the child and his parents and may be a focus out of which emerge emotional disturbances of far-reaching significance. Much can be done to make a child's illness an emotionally less traumatic and destructive event than it frequently is. Many things which happen to the sick child and contribute to current and future emotional disturbances are preventable if a little thought is taken and the child is looked on as a thinking, feeling, acting human being. If the physician is willing to go further and attempt to understand what illness itself may mean to the average child and what he feels about it, the emotional disturbances may be further minimized, and the total experience may be a constructive growth experience for the child.

When a child becomes ill many things happen to him which are strange and new and are poorly understood by him. He does not feel well, understands little of why he has become sick, is irritable, and perhaps wants to be left alone. His own anxiety is often intensified by that of his parents, who may become guilty and anxious about their own part in the production of the illness or their failure to have prevented it. The usual amount of parental concern and fussing may well be increased if the illness is not a clear-cut one. At such times the confusion of the child and his parents is then enhanced by the perplexity of the doctor.

When a child must be admitted to a hospital he has to face separation from his parents, his home, and all with which he is familiar and meet a new environment at a moment when he is handicapped by his illness, his confusion, and his anxiety. At such times even the most "normal" child is likely to want to cling to his parents, who are, after all, his natural pillars to lean on in times of stress. The more anxious and upset the parents are at these times, the more difficult it is for the child to separate himself from them.

Many children are brought to the physician poorly prepared for hospitalization, should it prove necessary. Often the parents assure the tense, anxious, ill child that he is going "just for an examination," only to have the plans changed by the physician who feels that hospitalization should take place. At these times the physician will often tell the mother that hospitalization is necessary and leave her entirely on her own to break the news to the child and to squirm out

occurs as a part of the personality reaction to almost any illness. This takes place in adults as well as in children. Regression takes place in the child as a defense against his anxiety and is dependent on the severity of the emotional disturbance and the length of the illness. Liess² has pointed out that the more severe regressions back to an infantile preoccupation with purely physical functions of food intake, metabolism, and excretion occur in the more prolonged or traumatic illnesses. He believes that this phenomenon may well be a technique of self-preservation in which all of the resources of the organism are marshalled to preserve life and energies and are not dispersed into nonessential activities. There is at the same time a similar preoccupation on the part of the medical attendants of the sick child in the fluctuations of the body temperature, respiratory and pulse rates, appetite, intestinal and urinary tract function, and symptoms, which contributes to but does not seem responsible for the child's regression back to a physical self-absorption. The younger the child at the time of the illness the more quickly the regression occurs. In general, the most recently acquired behavior habits and social techniques are the first to go. Finally, all expression of social relationships leaves and all that is left is a rather primitive insistence on and interest in food and affection. Symptomatically, what we observe in many sick children is an expression of emotional and social needs and outlets appropriate to a younger age period. The lusty boy of 9 years or so who in normal circumstances would as soon be found dead as crying, and who when he does cry yells vigorously, may under the stress of illness begin to whimper and mewl in the manner of an infant. Along with this comes a desire for affection and cuddling even in the public atmosphere of the hospital ward. In some children we observe the dramatic emergence of such infantile symptoms as thumb sucking, a baby-talk kind of speech difficulty, and enuresis. Masturbation especially is likely to occur after operations. In some older children a hypochondriacal preoccupation with bodily symptoms and functions may be a prominent part of the picture.

In the usual illness which is relatively short-lived this is likely to be transitory in nature. In children with some illnesses such as ulcerative colitis the regression to a highly infantile, dependent emotional state occurs quite rapidly early in the course of the disease and is more marked than the severity or duration of the disease process would lead us to expect. Here the severity of the personality disturbance which accompanies the disease process seems related to the basic personality structure and functioning of the child and is only partly a result of the way in which a sick child is regarded and handled. We have observed regressive reactions in children with slowly growing brain tumors who were brought for medical advice because of the personality change.³ None of these children with intracranial tumors was regarded by the family as having an organic illness at the time when they were brought for medical help. Euphoria, which is on occasion seen in adult patients with certain grave disease and which is usually regarded as having an ego protective function, is unusual in children in our experience.

that their placement in a convalescent home had some of the elements of being sent away because they were bad; this was especially true in those who were making a poor adjustment to the convalescent placement. The change in the adjustment of these children when they were helped to see that their illness and placement away from home were not in the nature of punishment was rapid. Some children are a little sheepish in owning up to fears that the illness is punishment and reveal these fears only after seeking reassurance that they will not be laughed at. One of our patients who had had several admissions to various hospitals and convalescent homes because of recurrent attacks of rheumatic fever with carditis, adjusted poorly on each hospitalization and placement. At the time she was seen she was irritable and demanding of extra attention from the nurses, she resented any attention paid to the other children on the ward, and she was insistent that her mother bring her toys and books at each visiting hour. These she rarely looked at once she had them. When her illness was discussed with her she gave the following reasons as to why she had become sick: "If you run and jump your heart beats fast so you get sick"; "One time I went sleigh riding and it tips over so you get a cold"; "I didn't obey my mother"; "You don't obey your mother and run out—you run up and down stairs"; (quite sadly) "It's my own fault I get sick"; she added rather tentatively, that fighting and disobeying caused one relapse in her illness. At least part of her behavior toward the hospital personnel and her mother seemed to have as its goal making sure that she was not being further punished.

Parental admonitions intensify any latent fear that the child may have that his illness comes as a punishment. Colds come because the child disobeys and does not wear his rubbers. A leg is broken because the child does not heed his mother's cautionary advice not to roller skate in the street. Upset stomachs could be avoided if the child would only eat what he is supposed to. Eyes are ruined by reading fine print or reading in poor light or from too assiduous attention to the comics. The warnings about what will happen are often supplemented with an "I told you so" when something does happen to the child. These are common statements by almost all parents and contribute to the child's idea that when he is sick he is being punished. The all too common practice of threatening the child with the doctor or with an operation if he continues to be bad (which to many parents means disobedience) lends further reality to the child's fears when he becomes sick and he is taken for medical advice. We have observed several children with hematuria associated with acute nephritis who were sure that they had caused the damage through masturbation. Their anxiousness was intense and interfered not only with their adaptation to the hospital routines but with their capacity to participate in the therapeutic regimen laid down for them. We can feel sure that in most sick children there is a certain amount of anxiety because of their ideas as to the cause of their illness and in many guilty feelings as to their own responsibility.

REGRESSIVE REACTIONS

Most observers are aware of the frequency with which some degree of psychological regression back to an earlier level of emotional and social adaptation

anxiety in the parent arising out of the illness of the child. This depends on the role of the child and his illness in the psychic economy of the parent. There may be a great deal of underlying hostility toward the child and guilt-laden feelings about this which bring out markedly unreasonable and irrational fears in the parent. There may be a marked need in the parent of an infantile love object; the fear of loss of the child through the illness intensifies the parent's anxiety and helps the child to maintain his regressive personality functioning brought on by the illness. The parent may have then relatively little impetus to help the child regain his previous level of maturity; the child's passive dependent infantile status fits so well into the parent's own underlying psychological needs. Other parents may feel guilty and anxious about their failure to have prevented the illness in the child, unrealistically believing that they should be able to prevent all illnesses in their children.

Whatever the factors in the parent which determine the degree of neurotic anxiety about the child's illness or which serve as triggers to release the anxiety, the intense emotional state of the parent tends to increase the emotional and social regression in the child and to perpetuate the reaction. To children with such anxious parents hospitalization and its attendant separation from the parent come as destructive, intensely traumatic experiences. The most difficult children to separate from the parents when hospitalization becomes necessary are those whose parents are torn with anxiety and are themselves fearful of being separated from the child. For these children, fortunately a relatively small percentage of those whom we have observed over a period of years, the ordinary ways in which we try to humanize the process of hospital admission and which are successful in allaying or preventing excessive separation anxiety in most children, are of little help. This group of hyperanxious parents and their emotionally disturbed children give considerable concern to hospital administrators, physicians, and nurses. The emotional problems in the child are as a rule of long standing but are made worse by the illness and the new emotional turmoil arising out of the illness in the child; the child is often severely enough upset emotionally that the treatment of his illness is hampered. The presence of the parent may allay some of the more recent intensifications of the emotional disturbance which arise out of the separation and hence aid in the clinical management of the sick child. The presence of an agitated and anxious parent, on the other hand, takes up an unconscionable amount of the time of the hospital personnel; the neurotically irrational nature of their surface concerns makes them unaffected by reassurance and explanation on a realistic basis. The presence of such parents complicates the diagnostic and treatment measures addressed to the child, their presence becomes disturbing to other children on the ward and most often such parents are asked to stay away, in self-defense, by the hospital authorities.

Clinical psychiatric experience with children shows that the exclusion of such parents, no matter how troublesome they are to the hospital staff and may appear to be to the sick child himself, may not be wise. When these children are seen at a later date the psychic trauma of the separation from the parents during the illness is seen as an event which further upsets the pattern of emo-

CONSTRUCTIVE RESPONSES

Some children respond to difficult situations in a constructive manner; to them an illness may cause minimal emotional disturbance. In fact, to many children a period of illness, if well handled by the parents, nurses, and physicians involved, may result in a constructive growth experience. All who have observed a large number of sick children in the hospital or in the home are familiar with the child who develops constructive compensations and comes out more mature than he was before he was sick. In this group of emotionally stable and healthy children it is rare to see intense separation anxiety if hospitalization is necessary. The parent-child relationships to which such children have been exposed have been, for the most part, healthy ones, and the parent, when confronted with the necessity of hospitalization for the child, does not respond with overwhelming anxiety which is communicated to the child. In the hospital, especially during the brief convalescent period before the child goes home, he makes friendships with other children on the ward and with the nurses. These friendly relationships often last long after the child leaves the hospital and goes back to his usual activities. The child often collects autographs from the hospital personnel and other child patients. When he is well enough he enters into the activities and routines of the ward and helps the charge nurse in various ways.

The convalescence of this group of children is a relatively easy one to supervise. Some of the younger children are able to work off some of the more normal anxieties associated with being sick through play. Doctor, nurse, hospital, or operation games are not infrequently seen in children who have been sick. The child whose premorbid patterns of dealing with difficult situations are constructive utilizes this form of play for only a relatively short time. In some less emotionally sound children prolonged preoccupation with this form of play is a symptom of the persistent unresolved anxieties.

PERSISTENT DEPENDENCY REACTIONS

There is another group of children who, more or less conditioned by the temporary security on an immature level which the illness has brought them, may try to perpetuate the infantile relationships to the environment which have given them a measure of spurious satisfaction. All of us who have had periods of hospitalization or severe illness are personally familiar with the let-down feeling which comes on leaving the hospital or resuming more normal activities. There are a few children who give up the secondary gains of illness most reluctantly even though they presented no particular symptoms of maladjustment prior to the illness. Children who were in an emotionally insecure state before their illness are especially likely to cling to these satisfactions. The attention, fussing, new toys and the like, although not appropriate satisfactions for their emotional needs, do tend to allay some of their anxiousness, no matter what the underlying causes.

The most persistent passive dependent infantile states which emerge out of the focus of a physical illness are those where there is a great deal of intense

for therapy and convalescence. Parental overconcern is the more important factor in most instances; this continues long after there is any need for a realistic concern about the effects of the illness and contributes directly to the child's continued preoccupation with bodily functioning.

The prolongation of sick-bed practices long after there is any reason is frequently seen. Some parents believe that something still is the matter with the child long after the period of convalescence has begun and at times long after it should have been complete. Other parents remain concerned not that something is the matter but that something might get to be the matter with the child. They are preoccupied with minor fluctuations in the temperature, weight, appetite, color of the skin, consistency of the stool; in fact, no aspect or function of the child is safe from the anxious inspection and concern of the parent. Often a careless word by the child's physician is seized on as justification for the marked concern. Pseudodiagnoses made by interested friends, teachers, nurses, and even at times by some physicians, fan the parental anxieties and lead to further overconcern. Such "diagnoses" are in the nature of "a touch of," "verge of," "if it had gone a little further it might have been," and the various types of "inward" manifestations of almost all diseases. Occasionally physicians thoughtlessly contribute to the development of this picture of chronic invalidism through overtreatment of what are essentially minor and self-limited diseases. At times they are more or less pushed into these unnecessary procedures by the aggressive, demanding attitude of the medically erudite, overanxious parent who presses with questions as to "Aren't you going to do this?" or "Why don't you do this?" The physician who gives in to these pressures has done his patient a disservice and has not helped the parents to approach the problem of illness in their child in a constructive way. It is unfortunately much easier to educate a child into the hypochondriacal invalid reaction than it is to lead him and his parents out of it.

MANAGEMENT OF CONVALESCENCE

The physician's responsibility to the sick child does not end with the cessation of the acute illness. An important part of the total job remains—the supervision of the convalescent period, which continues, except where the disease process leaves handicapping residuals, until the child is able to resume his former activities. During the convalescent period the physical changes caused by disease are repaired and the child returns to the level of maturity present before the illness.

The first step is stopping sick-bed practices when they are no longer necessary. The child is encouraged to participate more actively in his physical care and the number of times per day his temperature is taken is decreased. He is kept out of bed for increasing periods of time and encouraged to associate with other children. This reestablishment of personal relationships through group development of interests in the group activities the child gives up the increased personal attention from the nurse or mother, which was necessary while he was acutely ill, much more easily than when he is left to his own resources alone and apart from other children. It is a matter of common observation that chil-

tional and social growth and development in the child, and which, for the parent, serves as an additional focus for guilt, anxiety, and disturbed feelings which in turn lead to further functional aberrations of the parent-child relationship. In the light of clinical experience the best way of handling such situations would be, if at all possible, to let the parent remain with the child at least during the first day or two of hospitalization. Suitable isolation is necessary to lessen the ill effects of such an arrangement on the other children in the hospital. The unrealistic complaints and concerns of the parent should be handled with an awareness of what the underlying factors might be and an attempt should be made to deal with them on that basis.

It is certain, in the case of the emotionally disturbed child who becomes physically sick, that the period of the illness is a poor time to try to do much about his basic emotional disturbance; it is an equally poor time to add further avoidable stress to his already upset emotional life. During the illness, however, much can be done to help the disturbed parent and thus prepare the way for a more successful convalescence on the part of the child as well as for some direct help with his personality disturbance after he has sufficiently recovered from his illness.

There is a group of what we might term pseudo-anxious parents whose surface behavior is similar to that described above but is not rooted deep in their personalities. They seem to be responding to a particular cultural pattern which expects them to weep, wail, and cling to the child when he becomes ill without real conviction on their own part. They give up this form of reacting quite easily when someone in authority assures them that it is all right to act differently.

REBELLIOUS REACTIONS

Some other children handle the situation of illness and convalescence by developing resentments and rebellion against those who will not let them get back into the swing of things as soon as they would like to. They tend to blame others for the illness and their transient incapacitation. The management of the convalescent period is likely to be most difficult with these children, particularly if it is prolonged. The period of resentment and rebellion may begin almost at the outset of the illness or may start gradually or suddenly after the acute stage has begun to wane. This response in many of the children who exhibit it seems to be related to their anxiety over the theme of illness as a punishment. They often have fears of permanent injury as a result of the disease or operation and their behavior reaction serves to deny, in a compensatory manner, the presence of these fears.

CHRONIC INVALID REACTIONS

The hypochondriacal invalid reaction often follows an episode of physical illness. The illness need not have been a severe or a lengthy one. However, in some of the more drawn-out illnesses the child whose previous tendency is to have feelings of inadequacy and hopelessness, may develop rather alarming hypochondriacal responses which materially interfere with the over-all program

Convalescent Care

STANDARDS FOR CONVALESCENT HOMES FOR CHILDREN

PREPARED BY A SUBCOMMITTEE* OF THE COMMITTEE ON PUBLIC HEALTH
RELATIONS OF THE NEW YORK ACADEMY OF MEDICINE

FOREWORD

Standards for convalescent care were first formulated by the Committee on Public Health Relations of The New York Academy of Medicine in 1925. The section relating to the care of children was revised in 1934 to bring it into conformity with evolving pediatric practice. The far-reaching changes of more recent years have again made obsolete some of the earlier recommendations; hence the present restatement of the standards.

I. PURPOSE OF A CONVALESCENT HOME

A convalescent home for children should provide good institutional care in a physical and psychologic environment conducive to enhancement of physical and mental health.

II. NEED OF CONVALESCENT FACILITIES

The benefit which children derive from proper convalescent care is often more marked than is the case with adults. Children are naturally prone to recover from disease. Only a small proportion become long-term patients. With wise psychiatric guidance the emotional involvements of childhood can often be straightened out to prevent chronic invalidism.

The great majority of children in convalescent institutions come from homes where competent physical and psychologic handling is lacking. A convalescent institution, therefore, has the opportunity to provide a well-rounded therapeutic program which will prepare the children for a fuller life in their home surroundings.

This report is limited to the consideration of convalescence in institutions and does not deal with the placement of children in foster homes. The Committee suggests that foster-home care be carefully studied to determine its possibilities for expansion and improvement.

III. GENERALIZED HOMES

The fact that most convalescent homes accept children who are recovering from a wide variety of medical and surgical conditions is proof of the need for the generalized type of home.

IV. SPECIALIZED HOMES

The specialized type of home, with appropriate equipment and personnel, is needed for children requiring special care. In this group are patients suffering from cerebral palsy, orthopedic defects, neurologic conditions and rheumatic fever.

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dren on the hospital ward convalesce much more rapidly than do those isolated in separate rooms. Through group activities the child is eased back to reality by a repetition of the processes through which he has already lived in passing from one stage of his social and emotional development to another. There is a slight danger with some children when an over-enthusiastic physician or nurse, recognizing certain immaturities in a child, may try to push him too rapidly to a level of maturity which he had not attained before the illness. Liss believes that the school aged child benefits considerably in his convalescence if he is exposed to some of the learning processes, especially in the arts and crafts, which are more or less normal activities of this age. Through the resumption of normal living experience on a graduated scale the child finds his way back to health. Liss also believes that the knowledge and experience of the educator is of importance in dealing with these aspects of the child's convalescence. The hospital which has the services of a recreational or occupational therapist is most fortunate here even though many such individuals are quite lacking in ingenuity in finding stimulating and satisfying experiences for children of different age groups. There is too often a tendency to fit all children into the same type of activity and not to find out the individual needs and interests of the different children. In our own experience we have found the offices of the public school teacher assigned to the hospital invaluable in promoting convalescence in older children.

If the convalescence is to be carried out in the home the ingenuity of the physician and parent may be severely taxed to provide the opportunities for the child to reestablish his personal relationships through group activities which are in keeping with the state of the child's physical stamina of the moment, as well as to provide the other activities which will bring the child's interests away from his bodily functioning where they had retreated during the illness. If the convalescence is well handled with the full participation of both the parent and the child, there will be relatively few persistent pathologic personality reactions in the child. Attention to the parents' worries and concerns and what is behind them during the period of illness will be helpful in promoting a smooth return to health.

SUMMARY

Emotional disturbances in children often develop in the setting of physical illness. An understanding of the meaning of the illness to the child is helpful in the prevention of lasting emotional upset. To many children illness comes as punishment. A common psychologic reaction is a regression to an immature level of social and emotional adaptation. While many children react to illness in a constructive way, others may respond with persistent dependency patterns, rebellion, or chronic invalid reactions. Attention to the psychologic needs of the child during the convalescent period is also important in the over-all care of the sick child.

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1. Beverly, B. I.: Effect of Illness on Emotional Development, *J. PEDIAT.* 8: 533-43, 1936.
2. Liss, E.: Convalescence, *Mental Hygiene* 21: 619-622, 1937.
3. Langford, W. S., and Klingman, W. O.: Behavior Disorders Associated With Intracranial Tumors in Childhood, *Am. J. Dis. Child.* 63: 433-52, 1942.

6. Asthma of allergic or infectious origin

(Patients with wind-borne pollen allergies are not suitable for convalescent homes in rural areas)

7. Congenital syphilis (if long-term care is indicated)

8. Closed tuberculosis (i.e., pleurisy with effusion) if bed care is available

9. Chronic infections, e.g., chronic mastoiditis, osteomyelitis

It is impractical to specify the length of stay of patients suffering from these chronic diseases. If a patient's home is unsuitable for his return, he should remain in the institution as long as the care he receives there is superior to that which he might receive in his own home.

III. Malnutrition

A. Tuberculin-positive (no open or active lesions)

B. Tuberculin-negative

IV. Orthopedic disorders

A. Ambulatory patients who do not require specialized orthopedic treatment acceptable in any home

B. Bed and ambulatory patients who require special care in homes with special equipment

V. Emotional problems in which a neutral environment plus experience in group living under intelligent supervision might be beneficial

(Psychotic or feeble-minded children are obviously not included in this category. Only patients who exhibit symptoms which a competent diagnostician considers to be of basically psychogenic origin should be accepted. Homes which do not have competent psychiatric advice available should not accept children with emotional problems.)

VI. Preventorium care

Children who have been exposed to active tuberculosis in their homes may be admitted temporarily if they have shown negative reactions to tuberculin tests or positive reactions without active or open lesions. In the latter instance, an x-ray of the chest should be taken before admission.

In general, administrators should give preference to patients recovering from acute illnesses and should accept patients for long-term care only when there is a favorable prognosis.

Attention is directed to the fact that many institutions for convalescents also accept well children for vacation periods in the country, especially during the summer. This practice should be discouraged. Such vacations for well or almost well children are better provided by other agencies. Their exclusion helps to keep the standards of the strictly convalescent home at a high level.

Variations in seasonal occupancy may be obviated by affiliations with one or more hospitals to assure a steady flow of patients.

D. Transportation.—Whenever possible, one or both parents should accompany a child to the institution. If this is impossible, it is recommended that a representative of the institution meet the child and the parent at some convenient point. The opportunity is thus afforded for the parent to give the institution information about the child's behavior and background which may be helpful toward a satisfactory adjustment.

Institutions that admit both children and adults should, when possible, arrange separate times for admission of the two groups. The practice of transporting both groups at the same time may be accompanied by friction.

E. Records.—The Committee wishes to stress that records of the child's illness should arrive with the child. Too many children are admitted to convalescent homes with no indication whatever as to the type of treatment, medica-

V. ADMISSION

A. Policies.—A convalescent home should accept children under 2 years of age only if it has a nursery, and even then preferably for short-term periods. For these young children, foster-home care under competent supervision by responsible authorities is preferable.

Those above the age of 12 years require special personnel and facilities, and they should not be admitted to a children's convalescent home lacking these essentials.

Special dormitories should be available for boys and girls over 10 years of age. Sex segregation should not be maintained during work and play if adequately supervised.

There should be no discrimination on the basis of race, creed, or color.

Children should not be admitted to institutions for adults unless separate accommodations are available. The diet, daily routine, and the type of personnel for a children's home differ from those in a home for adults. Experience has shown that intermingling of the two groups detracts from the benefits to be derived by either.

B. Charges.—Since convalescent homes serve primarily those of the lower income groups, there should be no rigid regulations with regard to charges. The economic situation of each child's family should be investigated by a social worker, and the charge determined on the basis of the report and the probable period of care required. Children are sometimes discharged from convalescent homes before their condition warrants release because the prolonged stay strains the family resources. In such instances, rates should be adjusted.

C. Types of Patients.—For the guidance of administrators, who are frequently perplexed as to the suitability of patients for admission, the Committee has drawn up a list which may be helpful. The list is intended only as a guide.

TYPES OF PATIENTS SUITABLE FOR CARE IN GENERALIZED CONVALESCENT HOMES

I. Post-acute illness:

- A. Medical
- B. Surgical

II. Subacute and chronic illness:

A. Rheumatic disease:

- 1. Chorea
- 2. Rheumatic arthritis (low grade)
- 3. Cardiacs—functional classification of patients
 - a. Class I (patients with no limitation of physical activity) in any home
 - b. Class II (patients with slight limitation of physical activity) in any home
 - c. Class III (patients with marked limitation of physical activity) in homes with facilities for restricted activity
 - d. Class IV (patients unable to carry on any physical activity without discomfort) in homes with facilities for bed care

B. Diseases of long duration requiring special diets and medical supervision:

- 1. Diabetes mellitus (in the regulated stage)
- 2. Celiac disease (in the regulated stage)
- 3. Nephrosis (selected cases)
- 4. Colitis
- 5. Chronic skin disease requiring nursing care, e.g., eczema

Physicians trained in both pediatrics and psychiatry should be available on a consulting basis. In remotely located homes it may be possible to arrange with state mental institutions for the services of psychiatrists as consultants.

B. Medical Examinations.—Medical examinations should be made upon admission and discharge and as often as necessary in the interim. Long-term patients should be examined at least once a month.

C. Nurses.—There should be four graduate nurses to every fifty patient-beds and at least one graduate nurse in residence and on duty at all times, both day and night.

D. Attendants.—A convalescent home for children should provide at least one trained attendant for every ten patient-beds.

E. Dietitian.—An experienced dietitian should be on the staff to supervise the planning and preparation of general and special diets. In small institutions, arrangements should be made for the part-time services of a dietitian.

F. Recreational Therapist.—Every institution, irrespective of size, should have one staff member who supervises the children's recreation. The recreational therapist should be sufficiently well trained to be able to arrange varied activities according to the needs and abilities of the patients, always in close cooperation with the physician.

G. Teachers.—Provision should be made for children of school age whose convalescence is prolonged to continue their schoolwork while they are recovering their health. Teachers may be sent from local or state agencies, or they may be employed by the homes. The child's attendance at classes and the work required of him should be subject to the approval of the physician. Convalescent homes which accept bed patients should make arrangements for bed-ridden children to attend school if their physical condition warrants. The psychological advantage to a convalescing child of being able to continue his schooling can hardly be overemphasized. His social and psychological adjustment to normal life may depend upon his ability to rejoin his school class.

H. Ancillary Service.—The amount and type of ancillary service needed depend upon the type of patient admitted to the institution and upon the size of the institution.

As has been suggested earlier, employment of a full-time social worker is recommended for institutions whose size justifies the expense, and social service on some basis should be available to all homes regardless of size.

All convalescent homes should have psychologists and dentists on their staffs, at least on a part-time basis.

I. Kitchen Staff.—There should be cooks, waitresses and kitchen maids, the number to be determined by the size of the institution. In small institutions one person might fill all three positions. The planning of meals should not be left to the cook; presumably she has not had training in dietetics and would not understand the needs of the various types of patients.

J. Maintenance Staff.—The size of the institution will determine the number and type of maintenance personnel. Every institution will require at least one ward maid and one porter. Large institutions may need an engineer, an

tion, or diet they have been receiving. Absence of this important information may place the staff at a serious disadvantage if an emergency arises.

The Committee does not desire to specify in detail the form and content of the records of reference, but only to state that they should be as informative as possible in order that the staff may understand the background of the patient. If a convalescent home is associated with a hospital, the hospital record should accompany the child, and should be returned to the hospital, together with the report of convalescence, when the child is discharged from the home.

If an unaffiliated institution receives patients directly from a hospital, a full abstract of the hospital record should accompany the patient, and should remain with the record of convalescence at the home. When a patient is admitted from his own home, the family physician should prepare a comprehensive summary of the child's illness for the information of the convalescent home; this statement should accompany the child. In the last two instances, a report on the child's progress in the home should be forwarded to the referring hospital or physician.

F. Social Service.—Large institutions should employ at least one full-time social worker. A small institution should obtain at least the part-time services of a social worker. Two or more homes in adjacent areas may arrange to share the services of one worker. Small homes in isolated areas may be able to "borrow" social service or visiting nurse service from public agencies.

The social worker at the convalescent home or the visiting nurse acts as a liaison officer between the parents and the institution. Her initial interview with parents of a convalescent child and the hospital social worker should elicit information not only on the economic status of the family, but also on the child's background. Such knowledge may be helpful in preparing the way for proper adjustment in the home. The social worker has other important duties when the child is discharged; these are discussed under Discharge Policies.

G. Examinations.—A physician should examine each new patient within twenty-four hours of admission, if he does not come directly from a hospital. When a patient is admitted directly from a hospital, the examination should be made not later than forty-eight hours following arrival.

It is impractical to isolate patients prior to the admission examination. Few institutions have proper facilities for isolation and, furthermore, certainty of the absence of communicable disease would, in some instances, require isolation for as long as four weeks. Air sterilization affords a more effective and practical method of controlling the spread of communicable disease than the maintenance of facilities for isolation.

VI. MEDICAL SUPERVISION AND CARE

A. Physicians.—During recovery from illness, children should have competent medical supervision. Every convalescent home for children should have on its paid staff a well-trained physician, preferably a pediatrician. A volunteer medical staff sometimes takes its responsibilities too casually. Moreover, it is important for the administrative and medical staffs to work in close cooperation if patients are to receive the best possible care.

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E. Dietitian.—An experienced dietitian should be on the staff to supervise the planning and preparation of general and special diets. In small institutions, arrangements should be made for the part-time services of a dietitian.

F. Recreational Therapist.—Every institution, irrespective of size, should have one staff member who supervises the children's recreation. The recreational therapist should be sufficiently well trained to be able to arrange varied activities according to the needs and abilities of the patients, always in close cooperation with the physician.

G. Teachers.—Provision should be made for children of school age whose convalescence is prolonged to continue their schoolwork while they are recovering their health. Teachers may be sent from local or state agencies, or they may be employed by the homes. The child's attendance at classes and the work required of him should be subject to the approval of the physician. Convalescent homes which accept bed patients should make arrangements for bed-ridden children to attend school if their physical condition warrants. The psychological advantage to a convalescing child of being able to continue his schooling can hardly be overemphasized. His social and psychological adjustment to normal life may depend upon his ability to rejoin his school class.

H. Ancillary Service.—The amount and type of ancillary service needed depend upon the type of patient admitted to the institution and upon the size of the institution.

As has been suggested earlier, employment of a full-time social worker is recommended for institutions whose size justifies the expense, and social service on some basis should be available to all homes regardless of size.

All convalescent homes should have psychologists and dentists on their staffs, at least on a part-time basis.

I. Kitchen Staff.—There should be cooks, waitresses and kitchen maids, the number to be determined by the size of the institution. In small institutions one person might fill all three positions. The planning of meals should not be left to the cook; presumably she has not had training in dietetics and would not understand the needs of the various types of patients.

J. Maintenance Staff.—The size of the institution will determine the number and type of maintenance personnel. Every institution will require at least one ward maid and one porter. Large institutions may need an engineer, an

electrician, a gardener, a carpenter, and others. Small institutions can probably combine all of these functions in one or two persons.

In planning occupational therapy for the children it may be possible to employ members of the maintenance staff as teachers if they have been carefully selected. Any time lost by a worker in using the children as "helpers" may be well worth while if it enhances the children's morale by making them feel useful. Such work therapy should be carried out only with the full knowledge of the physician and under his direction as to the amount and type of "help" which may be given by the patient.

K. Volunteers.—Admittedly the standards here formulated may not be attained without extensive changes in present practices. The element of cost has not been discussed because wide variations in local conditions preclude any general statement of this item. It is recognized, however, that expense may be a deterrent to the realization of many of the recommendations here set forth. It is suggested that community support for the work of convalescent homes should be enlisted in every way possible. Such support might be expressed not only through financial contributions to the institution, but through an active program for recruitment of volunteers who may give valuable service under the supervision of the trained staff. Volunteer help may be used at various levels of service, such as nursing, recreation, social work, transportation, and general housekeeping.

VII. REGIMEN

The details of the daily program should naturally vary with the physical condition of the children. Those needing but a short convalescence could probably be more active than those requiring a longer period to regain their health. A routine of sufficient variety to hold interest should be mapped out for each child.

The regimen should be properly balanced as to rest, play, exercise, and therapy, with some free time each day for elective activity within the limitations of the child's physical condition. A rest period of from one to two hours should form part of the daily routine. Rest periods will require supervision as much as will the play, work, and exercise periods, but care should be taken to avoid rigidity and militarism in the supervision of any activity.

VIII. DIET

A high level of nutrition should be maintained by providing sufficient wholesome, nourishing food, properly cooked and attractively served. The best balanced meal in the world is of no value if it is left on the plate because of improper preparation. It is particularly important that food should be of the proper temperature. In institutions for children, small "treats" in the diet may serve a useful psychological purpose.

The matter of eating between meals should be left to the discretion of the physician. Extra nourishment may be essential for some children, perhaps in small meals at frequent intervals.

It goes without saying that the physician is the arbiter who prescribes special diets, and the dietitian should be sufficiently trained to plan and arrange them.

IX. TEACHING POSSIBILITIES

Many institutions do not make use of the excellent opportunity they have to inculcate health habits in the children and to teach them rules of hygiene and health. Stressing the importance of fresh air, sunshine, rest, and a proper diet in their everyday routine is a practical way of teaching them how to live and how to keep well.

It is the duty of every convalescent home to train the children under its care to a daily routine, thus starting good habits which may continue after discharge. The children should become accustomed to regular lives and to the practice of good health habits.

In addition to the valuable work which a convalescent home can do in teaching children proper habits of health and hygiene, it can also render an important service in the training of student nurses and interns. The presence of such personnel would be valuable to the home, and the opportunity to observe convalescent patients would be advantageous to the students.

X. RECORDS

Few institutions keep proper records of the children in their care. Some make no attempt to keep any medical or health record other than the diagnosis on the admitting slip and a notation of the child's weight; in many instances, the weight records are kept in a separate book. A carefully kept history of a patient's progress in a convalescent home would be of great value in the event of a later illness. Good records are also of incalculable value for research.

Assuming that a comprehensive history of the child's illness and treatment is presented at the time he is admitted to the institution, the convalescent home should add to it all the important facts of the child's progress during his stay in the home, including his psychology as well as his physical adjustment. A detailed history should be kept of any illness which occurs while the patient is in the convalescent home.

XI. VISITING

Rules regarding visits to patients should not be rigid. The size of the convalescent home, the type of patients admitted, and the age of the patients will undoubtedly be determining factors in the formulation of the rules.

Since the welfare of the patients should be the first concern of the convalescent home, the psychology value of frequent visits by the patient's family should be carefully weighed against the possible danger of contagion.

XII. DISCHARGE POLICIES

The discharge of a patient should be authorized by the physician in charge. This decision should not rest with the superintendent, as it does in many institutions at the present time.

As has been stated in a previous section, a patient should not be discharged because of inability to pay; the financial status of the family should be studied and a rate of payment agreed upon which makes possible the optimum stay in the home.

The aim of convalescent homes should be the attainment of optimum care and improvement in the health of children, and this aim should not be sacrificed by the admission of too many patients in relation to facilities and personnel.

Whenever possible, the institution's social worker or a public health nurse should visit the patient's own home prior to his discharge to determine whether discharge to that home is advisable. Investigation may reveal an acute illness or some other remediable condition which a relatively short additional stay in the institution would enable the child to avoid.

It is desirable for parents to take a child from the institution, but when this is impossible, the transfer should be made by the social worker or by a public health nurse.

When a long-term patient is discharged, the institution should furnish to the authorities of his school a report of the child's progress in his schoolwork while in the home. Such a report will assist the authorities in placing the child in the proper group when he returns.

XIII. FOLLOW-UP PROCEDURES

The social worker or a public health nurse should visit the patient's home when he is discharged and should make an additional visit from three to six months later in order to evaluate the patient's progress and the benefit derived from his stay in the institution. A report of this follow-up visit should be filed with the complete record of the case. The interval between the discharge and the date of the follow-up visit would be determined by the type of illness for which the patient was admitted to the institution.

XIV. PLANT

Some maintain that convalescent institutions for children should be located in rural and semirural areas in order to supply a maximum of fresh air, sunshine and freedom of movement. Others are of the opinion that such institutions should be located in urban areas, where they may have the advantage of readily available hospital staffs and facilities. Suburban communities would meet the need for fresh air, sunshine and freedom of movement, and at the same time the distance from hospitals would not be so great as to discourage visits by consulting physicians, and the transportation to hospitals for special treatment could be arranged without too great difficulty.

The optimal capacity of a convalescent home for children is from fifty to seventy-five beds. The Hospital Facilities Section of the United States Public Health Service has worked out plans which afford assistance to those concerned with the construction of convalescent institutions. The proportion of beds to be allotted to patients requiring long-term care is a matter of policy on the part of each institution.

XV. RESEARCH

The basic facts of convalescence are not well established. There is a well-recognized need for research on the clinical and biochemical, as well as the organizational and social aspects of convalescence. It should, however, be emphasized that adequate research cannot be undertaken without proper facilities.

personnel, record-keeping, and funds. Since few convalescent homes for children possess all these advantages, research programs should be instituted only in homes having the proper staff and facilities to conduct well-thought-out programs.

XVI. GRADING AND LICENSING

Nowhere in the country is there adequate supervision over convalescent homes. A number of states now have laws requiring that hospitals and related institutions be licensed, but the requirements vary from state to state. In some states the licensing is done by the departments of welfare; in others, by departments of public institutions or departments of health. Official inspections of convalescent homes are, as a rule, limited to the physical plant; little or no attempt is made to gauge the quality of care rendered. Every state should include convalescent homes among the institutions for which licensing is required and should provide for adequate qualitative inspections of these homes.

Comments on Current Literature

Q FEVER

TWO naturally occurring outbreaks of Q fever have been reported in the United States, the first in Amarillo, Texas, in March, 1946, and the second in Chicago, Ill., in August, 1946. Both sharp outbreaks occurred among slaughter-house workers who had come in contact with tissues and body fluids of infected cattle or sheep. An arthropod vector did not seem to be involved in these American outbreaks, as apparently had been the case in other outbreaks. Infection of human beings presumably occurred by direct contact or by means of droplets of splattered fluids. However, in these two explosive and isolated outbreaks, the manner in which the animals had become infected was not determined, nor was it possible to gain a clear idea of the natural reservoirs of Q fever in the United States.

The occurrence of Q fever in an apparently endemic area in California offered opportunity for further study of this rickettsial disease. In the June issue of the *American Journal of Public Health*, Shepard and Huebner¹ report studies concerned with the occurrence of Q fever in Los Angeles County in the so-called milk shed area situated ten to thirty miles southeast of the center of the city. In this endemic area, the diagnosis of Q fever was based on typical clinical history and on confirmatory laboratory findings. In their report, Shepard and Huebner¹ give as the typical clinical history the following:

"The onset was acute with fever, headache, chills or chilly sensations, and body aches and pains. Cough was frequently complained of but was not a prominent symptom. The sputum which was sometimes produced was at times blood-tinged. Chest pain was common and was usually of a lateral distribution, although a feeling of substernal congestion was frequent. Physical examination of the chest often revealed little of note except perhaps suggestive findings. Respirations were elevated when pneumonic involvement was extensive. Roentgenography revealed a pneumonic process which was usually diagnosed as "atypical" pneumonia when patchy, and "early lobar" pneumonia when diffuse. The leucocyte count tended to be normal or slightly elevated. The illness ran a course of one to three weeks' fever with prolonged convalescence especially in older patients. No deaths were found which could be attributed to Q fever."

Confirmatory laboratory diagnosis includes demonstration by complement-fixation serum tests of type-specific antibody, especially increasing titer during clinical recovery, and isolation of the etiologic agent, *Rickettsia burneti*, from the blood during acute illness.

Seventeen human cases of Q fever were diagnosed in the Los Angeles area. Although none of the clinical cases occurred in dairy workers, all but two patients gave a history of having visited dairies or of having lived near them. On the other hand, one-half of the dairy workers tested were shown to have positive complement fixation tests for *R. burneti*. The lack of clinical manifestations or of history of illness in these subjects suggested that many had undergone mild or inapparent attacks of Q fever.

From an epidemiological viewpoint it is significant that sixty sera of beef cattle from Texas and adjacent states and more than sixty sera from Maryland milk cows were found negative for complement fixing antibodies for Q fever, whereas of 130 bovine sera from the Los Angeles area, 21, or 16.2 per cent were

found positive. However suggestive, these results do not make it possible for the authors "to state definitely that the cows are the source of human Q fever infection, since the possibility remains that the same source infected both cows and man."¹

In this connection, a paper by Huebner, Jellison, Beck, Parker, and Shepard,² reporting the isolation of *R. burneti*, the causative agent of Q fever, in samples of raw milk from four dairies in southern California, suggests another possible mode of transmission. Pasteurization, even under field conditions, apparently rendered naturally infected milk noninfectious for guinea pigs. However, these authors state that available epidemiological evidence does not indicate that the drinking of milk was the cause of a majority of the cases thus far studied.

In searching for specific therapy of Q fever, Hottle and Huebner note that streptomycin has been found to exercise rickettsiostatic action on the causative organisms of epidemic typhus, endemic typhus, Rocky mountain spotted fever, and rickettsialpox. In the March 19th issue of the *Public Health Report*, Huebner and Hottle³ report that streptomycin exerts a rickettsiostatic action on *R. burneti* in experimental infection of embryonated eggs and guinea pigs. Of particular interest were their results with guinea pigs. Although the number of animals used was small, it was shown that nineteen of twenty-four guinea pigs receiving subcutaneously 40 to 50 mg./kg. of body weight of streptomycin three or four hours after a large inoculation of *R. burneti* survived, whereas twenty-seven of the twenty-eight controls not receiving streptomycin died.

The complete reporting of Q fever must depend upon increased awareness of its presence by physicians and the adequate use of laboratory diagnostic facilities. Further studies of Q fever promise to clarify the natural history of the disease and will afford opportunities for possible control. As more work is done with rickettsiostatic and rickettsiocidal agents, particularly the newer antibiotics, adequate therapy of rickettsial diseases, including Q fever, will be forthcoming.

RUSSELL J. BLATTNER.

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News and Notes

The Transactions of the Fifth International Pediatric Congress, held in New York, July, 1947 will appear in Vol. XXXVI of *Acta Paediatrica*. Price 25 Swedish crowns. Orders should be sent to the following address: Acta Paediatrica, Polhemsgatan 30, Stockholm, Sweden.

General Index to Vols. I-XXX of *Acta Paediatrica* has been published and may be obtained for 15 Swedish crowns.

The pediatricians in the Union of South Africa have formed the South African Paediatric Association. It is formed within the Medical Association of South Africa and has been recognized by the Federal Council of that association. The Chairman is Dr. Basil Melle, and the Secretary-Treasurer, Dr. Seymour Heymann.

The Kaiser medal for outstanding medical service was awarded to Dr. John Aikman, assistant professor of pediatrics at the University of Rochester School of Medicine, by the Rochester Academy of Medicine on May 4.

At the annual meeting of the American Pediatric Society, held in Quebec in May, the following officers were elected:

President: Jean V. Cooke, St. Louis

Vice-President: Lawson Wilkins, Baltimore

Secretary-Treasurer: Henry G. Poncher, Chicago

The Second International Symposium on Feelings and Emotions is being sponsored by the Loyal Order of Moose, with the cooperation of the University of Chicago, on October 28, 29, and 30. Dr. Martin L. Reymert, Director of the Mooseheart Laboratory for Child Research, is General Chairman, and Dr. Anton J. Carlson, professor emeritus of physiology at the University of Chicago, is Honorary Chairman. From forty to fifty scientists will contribute to the discussion at Mooseheart, Ill., among whom will be:

John E. Anderson, The University of Minnesota

Chester Darrow, Illinois Institute for Juvenile Research

John Elmgren, University of Gothenburg, Sweden

Arnold Gesell, Yale University

Harold Jones, University of California

James G. Miller, University of Chicago

Detailed information can be obtained by writing Dr. Reymert at Mooseheart, Ill.

The Department of Pediatrics, Washington University Medical School, announces a two-month refresher course, September through November. The entire field of pediatrics will be covered. The course will be given at the St. Louis Children's Hospital, fee \$200. Detailed information may be obtained from the Director of Post-Graduate Studies, Washington University School of Medicine, 4580 Scott Avenue, St. Louis 10, Mo.

The American Academy of Pediatrics' Committee for the Improvement of Child Health will take over their new office at The Children's Hospital of Philadelphia, 18th and Bainbridge Streets, on July 1. Dr. John P. Hubbard is Director of this Committee. In addition to his work with the American Academy of Pediatrics, Dr. Hubbard will conduct a rheumatic fever teaching program throughout Pennsylvania under the auspices of the State Health Department.

Book Reviews

Psychopathology and Education of the Brain-Injured Child. Alfred A. Strauss and Laura E. Lehtinen, New York, 1947, Grune & Stratton, pp. 206. Price \$5.00.

This book is certainly required reading for anyone who undertakes the education of children with cerebral palsy or other cerebral difficulties. The discussion is properly concerned with the psychologic factors which modify educational plans. The handling of this part of the problem is skillful and authoritative. The selection of appropriate tests is discussed, and the authors point out the dangers of relying on tests which are adapted to unhandicapped children.

The medical discussion is, this reviewer believes, less adequate than other parts of the volume, but certainly one major point is important and relevant. The concept that deviations from normal development should be recognized is obviously correct. Pneumoencephalography and electroencephalography are hardly discussed at all, and pathology is discussed casually and without much curiosity. The orthopedic implications are also treated briefly.

After all, the authors were interested in the methods by which children could be educated, in the face of irregularities of mental function. The discussion of this major problem is full, reliable, and helpful. Certainly no other publication gives any such information. The great virtue of the book is that it reports the viewpoint of experienced psychologists and teachers in a field which has not been adequately explored by medical men.

B. C.

Infant Nutrition. P. C. Jeans and W. McKim Marriot, ed. 4, St. Louis, 1947, The C. V. Mosby Co., 516 pages. Price \$6.50.

A new edition of what has become since its publication in 1930 one of the standard medical texts for students and practitioners. In this edition the name of Dr. Jeans, who prepared the third edition in 1941, rightly becomes the senior name to the text.

The fourth edition has been completely revised and many parts rewritten in keeping with the developments in nutrition which have taken place in the last seven years. Some of the illustrations, such as those showing techniques, are new and in keeping with recent advances. All in all, it is a most satisfactory text and will undoubtedly continue to hold the place it has made for itself in the past.

Year Book of Pathology and Clinical Pathology. Howard T. Karsner, M.D., and Arthur H. Sanford, M.D., Editors, Chicago, 1948, Year Book Publishers, 558 pages. Price \$3.75.

This is the first Year Book on pathology to appear since 1941. Dr. Karsner and Dr. Lund, his associate at the Institute of Pathology of Western Reserve University, have selected their material from the most recent literature of pathology rather than attempting to cover the interval since the last edition. Over 200 pages of the text are on Clinical Pathology, edited by Dr. Sanford of the Mayo Foundation, who has followed the same principle. All of the most recent advances in methods are included.

The Baby's First Two Years. Richard M. Smith, M.D., Boston, 1948, Houghton-Mifflin Company, 181 pages. Price \$2.75.

A revised, and in many parts rewritten, text of one of the pioneer books on infant care for mothers. The material reflects the many years of Dr. Smith's experience in prac-

tice in that it presents what the average mother wants and needs to know about her baby. The author has kept pace with modern trends and developments in infant care and it is a safe and sane text for parents. Out of curiosity the reviewer compared it with one of the earlier editions of nearly twenty-five years ago (it was first published in 1915), and the changes it revealed which have taken place in pediatrics in the last quarter century are most interesting.

Nursing of Children. Gladys Sellew, R.N., Ph.D., in collaboration with Sisters Annette Walter, M.A., and Ann Harvey, M.A., ed. 6, Philadelphia, 1948, W. B. Saunders Co., 486 pages.

The fact that this is the sixth edition of Sellew's text on pediatric nursing since it was first published in 1926 is evidence that it has found a definite place in nursing education. The book contains a little bit of everything about children and the care of children. In fact, the chief criticism is that it is too expansive and the important is mingled with the unimportant. It contains far more than the average student nurse needs to know or should be expected to know. The text strolls far from the subject of the nursing of children. A careful and judicious pruning of the book, to about two-thirds of its present size, would make it much more useful.

Editor's Column

AN EDITORIAL PROBLEM

ONE of the more difficult problems that comes to the editorial board of a medical journal is the question of papers which either contain new ideas, or report work in which the conclusions are quite at variance with currently accepted viewpoints or practices. This is particularly true when the point of the paper has to do with therapeutic procedures.

Some contend that the publication of such papers puts the stamp of approval of the Editorial Board on the conclusions and findings. If this view were to prevail it would result in nearly every new idea being buried. The other viewpoint is that the work will stand or fall on its merits; if the conclusions are substantiated by subsequent studies by independent workers, much has been accomplished; if for some reason the work is not substantiated, no real harm has been done. An editorial board is not a scientific research group with the function of testing out new ideas before they are published, but it does have a definite responsibility in accepting papers of this nature for publication. There are certain criteria which a board must use. First of all, the conclusions must be logical deductions from the work upon which they are based. A matter of further importance is the recognized scientific integrity of the author or the clinic where the studies were made. We could cite numerous illustrations from medical history where papers have been rejected because they presented ideas contrary to accepted current practice, and later these new ideas or conclusions have proved to be correct. On the other hand, many illustrations come to mind where the ideas or conclusions drawn have turned out to be erroneous.

This discussion has been brought about by the recent acceptance and publication of a number of articles in *THE JOURNAL OF PEDIATRICS* which fall into this category, for example, the work on the feeding of infants with diarrhea in last month's issue from Dr. Holt's clinic in New York. Most certainly this procedure needs a thorough check by other clinics and investigators before its value can be established or the practitioner can change from the initial starvation period which is the accepted practice of many years. We are sure no one will question the propriety of the publication of the studies by Dr. Holt and his associates, nor would anyone consider the publication to imply that the members of the Editorial Board of the *JOURNAL* were urging a complete volte-face in the handling of infants with diarrhea. This paper will recall to the older pediatricians the furor that was caused a number of years ago by Coleman and DuBois, who fed their patients with typhoid fever, in contrast to the starvation diet which had been the accepted method of treatment for several

decades. Also in July issue of the JOURNAL, Dr. Adams, a younger and less well-known pediatrician, presented the results of a rather startling simplification of the feeding of premature infants which he experimented with largely by necessity during the war. Again the Editorial Board feels independent confirmation is necessary before the practitioner should turn from accepted methods to these simpler methods.

These are two examples of a number of papers with new ideas and procedures contrary to accepted practice which the Editorial Board of the JOURNAL has accepted for publication. It does not mean that the Editorial Board officially sponsors or advocates the new procedures. The board has, however, the responsibility of presenting new ideas and procedures in the interest of medical progress, even though ultimately the conclusions or work of the authors are found to be faulty. The JOURNAL has rejected papers presenting new ideas when it was felt the conclusions were not warranted by the work upon which they were based, and a few were rejected when, in the opinion of the board members, the proposed procedures carried an element of danger. The Editorial Board of the JOURNAL feels that its readers have the intelligence and judgment to form their own opinions, and that they not only appreciate but desire the stimulation of new ideas which reflect the intellectual curiosity upon which scientific progress depends.

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Original Communications

HYALURONIDASE IN FLUID ADMINISTRATION

A PRELIMINARY REPORT

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THE administration of fluids to infants and young children has always been a problem. To give them intravenously frequently meant a cutdown which involved further trauma to a usually very sick infant, and even that was at times difficult in cases of circulatory collapse and shock.

Subcutaneously, fluids could be given easily enough but not in great enough quantities nor repeatedly in the same area, due to the great distention and trauma to the tissues.

Certainly a method or drug to facilitate elysis would be helpful to the pediatrician treating dehydrated babies. Recently several hopeful reports¹⁻³ have appeared on the use of hyaluronidase, a drug which may be the answer to this problem.

In their papers Sannella¹ and Hechter² showed that this enzyme increased the rate of fluid absorption twelve times. This action was explained by the fact that hyaluronidase, a mucolytic enzyme,⁴ acts on and depolymerizes the mucopolysaccharide, hyaluronic acid. This is the gel present in the ground substance of connective tissue, which acts as a tissue barrier to fluid diffusion.

In Sannella and Hechter's work on rabbits,^{1,2} guinea pigs,³ and twelve human volunteers,² the only untoward effect noted was a slight transient erythema at the site of injection, occurring a few hours after use and associated with a dull, aching pain. However, in these reports only the effect on the blood count, blood pressure, and pulse was studied.

Since this drug^{*} has tremendous potentialities in fluid administration, it was decided that further and more detailed studies should be undertaken to determine the full safety of the drug and to determine whether it would make elysis potent enough to decrease the number of intravenous injections necessary.

First, six individuals (four children and two adults) were studied from the standpoint of the effect of hyaluronidase administration on the urine, blood

From the pediatric service of New York Medical College, Flower-Fifth Avenue Hospitals, and Metropolitan Hospital, New York, Dr. Reuel A. Benson, Director.

*The hyaluronidase was supplied through the courtesy of Dr. J. C. Winter, Director of Clinical Research of G. D. Searle Co., Chicago, Ill.

count, sedimentation rate, cholesterol, phosphorous, proteins, urea nitrogen, creatinin, sugar, ieteric index, van den Bergh, and cephalin flocculation tests.

These tests were done before and twenty-four hours after the administration of 0.02 mg. (0.2 c.c. of 100 μ g per cubic centimeter) of hyaluronidase to each individual, and the results are summarized in Table I.

TABLE I. EFFECT OF HYALURONIDASE INJECTIONS

	BEFORE	AFTER
Number of subjects	6	6
Sugar	94-111 mg. %	83-119 mg. %
Urea	12.4-19.5 mg. %	10.6-17.5 mg. %
Creatinin	1.2-1.8 mg. %	1.3-1.7 mg. %
Ieteric Index	4-5 units	4-5.2 units
Van den Bergh Test	Negative	Negative
Cephalin	Negative	Negative-1 plus
Phosphorus	2.4-4.2 mg. %	2.4-5 mg. %
Phosphatase	1.8-7.7 Bodansky units	2.9-12 Bodansky units
Total Cholesterol	117-193 mg. %	140-195 mg. %
Free Cholesterol	17-45 mg. %	41-60 mg. %
Cholesterol Esters	88-156 mg. %	90-154 mg. %
Total Serum Proteins	6.9-7.9 Gm. %	6.7-8.3 Gm. %
Globulin	2.1-3.4 Gm. %	1.7-3.6 Gm. %
Albumin	3.9-5.8 Gm. %	4-6.8 Gm. %
A/G Ratio	1.1-2.8	1.1-3.2
Urine	Negative; rare hyaline casts	Negative; occasional hyaline casts

As far as could be determined, there were no harmful effects from the tests made. However, in three of the patients the cephalin flocculation test became one plus and a few hyaline casts appeared in the urine.

In view of this, the urine of ten children was examined before and then checked twenty-four hours after the injection of 0.02 mg. (0.2 c.c. of 100 μ g per cubic centimeter) of hyaluronidase given on three successive days. The results are listed in Table II.

TABLE II. EFFECT OF HYALURONIDASE ON URINE

CASES	BEFORE INJECTION	AFTER FIRST INJECTION	AFTER SECOND INJECTION	AFTER THIRD INJECTION
1	Neg.	Alb.	Neg.	Neg.
2	Neg.	Neg.	Neg.	Neg.
3	Alb.	Neg.	Neg.	Neg.
4	Alb.	Neg.	Neg.	Neg.
5	Neg.	Neg.	Neg.	Neg.
6	Neg.	Alb.	Neg.	Neg.
7	Alb.	Alb.	Alb.	Neg.
8	Alb.	Alb.	Neg.	Neg.
9	Alb.	Neg.	Neg.	Alb.
10	Neg.	Neg.	Neg.	Neg.

It can be seen from this limited study that hyaluronidase had no harmful effects on the kidney, according to urine examinations.

Cephalin flocculation studies also were done on six children before and after the injection of 0.02 mg. of hyaluronidase. Again the findings revealed that there were no harmful effects.

Various dilutions of the drug were tested to see what variations there were and to decide which dilution would best suit the purpose for fluid administration and skin testing.

Two groups of medical students and one group of normal infants were tested by intradermal injections of 0.2 c.c. of various concentrations of hyaluronidase, and the absorption time determined. The results are shown in Table III.

TABLE III. HYALURONIDASE DILUTIONS PER CUBIC CENTIMETER

NUMBER OF PERSONS	1 MG. (TIME IN SEC.)	$\frac{1}{10}$ MG. (TIME IN SEC.)	$\frac{1}{100}$ MG. (TIME IN MIN.)	$\frac{1}{1000}$ MG. (TIME IN MIN.)	$\frac{1}{10,000}$ MG. (TIME IN MIN.)	NORMAL SALINE (TIME IN MIN.)	M/6 LACTATE (TIME IN MIN.)
5 Adults	36	88	8	21	25	59	65
7 Adults	32	84	7.5	14.5	23.5	60	63
5 Children	29	92	7.3				

It can be noted that as the solution was diluted, the time required for absorption of the fluid increased proportionately. It was felt that the $\frac{1}{100}$ mg. of hyaluronidase per cubic centimeter would be the best dilution to use for skin testing from the standpoint of accuracy and safety because:

1. The variation between the groups tested with this dilution was minimal.
2. Fluid absorption was not too rapid so that better control could be maintained, and yet it was not slow enough to delay the progress of the tests too long.
3. Sensitivity was just as marked with this dilution as with greater concentrations, and therefore it would be safer as well as more economical.

Having decided on the strength of solutions to use and since hyaluronidase had no discernible harmful effects on any of the individuals, a study of sensitivity was undertaken.

One hundred and eight skin tests were done using 0.002 mg. (2 μ g) per dose. The procedure followed was the intradermal administration on the forearm of 0.2 c.c. of a solution containing 10 μ g Hyaluronidase per cubic centimeter. Of seventy-nine children, seven had positive reactions, or 8.9 per cent. Of twenty-nine adults, three had positive reactions, or 10 per cent. In the total group, there were ten positives or a 9.3 per cent incidence of reaction.

A positive reaction consisted of a wheal with pseudopods appearing within five minutes, persisting for twenty to thirty minutes and associated with itching.

Since the hyaluronidase still contained impurities, a more purified extract was obtained and tried on two of the positive reactors. The reactions remained positive. Thus, the percentage of positive reactions just given would hold until a more purified product can be obtained.

The degree of pain associated with elysis, both with and without hyaluronidase, was next studied. Clyses of 70 c.c. were given into the anterior aspect of the mid-thigh of each of two volunteers. The needles were inserted into what appeared to be identical areas. Then 20 c.c. of a solution of 1 μ g of hyaluronidase per cubic centimeter in normal saline were given on one side and 20 c.c. of normal saline on the other. Then an additional 50 c.c. of normal saline were given on each side.

Dull pain was experienced on both sides, but it disappeared more rapidly on the hyaluronidase side, where it lasted two minutes and the swelling was gone in eight minutes. On the other side, there was prolonged dull pain and swelling, which lasted one hour.

In addition, the urinary output was checked on the day of the test and compared with that of the day before and after. No definite consistent alteration in output could be detected.

Studies relative to the effect of this product when added to adrenalin, penicillin, procaine, and streptomycin were done, and in each case the hyaluronidase facilitated absorption, as illustrated in Table IV.

TABLE IV. EFFECT OF HYALURONIDASE ON ABSORPTION OF MEDICATIONS

SOLUTION	TIME IN MINUTES	
	NO. OF PATIENTS	
	5	11
Hyaluronidase in Saline	5-9	5-11
Streptomycin and Hyaluronidase	5-9	
Streptomycin in Saline	50-70	
Adrenalin in Saline	40-65	
Adrenalin and Hyaluronidase		8-17
Procaine and Hyaluronidase		6-12
Penicillin and Hyaluronidase		5-10

Following these studies, hyaluronidase was tested on patients with various conditions such as acute infections with elevated temperatures, allergies, and rheumatic fever. To these patients, 0.2 c.c. of 100 μ g per cubic centimeter was given intradermally and the time of absorption noted. The results are given in Table V.

TABLE V. EFFECT OF HYALURONIDASE IN SALINE ON VARIOUS CONDITIONS

CONDITION	NUMBER OF PATIENTS	NUMBER OF MINUTES FOR ABSORPTION
Elevated Temperature	10	4-8
Allergies	10	5-9
Rheumatic Fever	6	5-11.

As can be seen from Table V, the rate of absorption was fairly equal in all types of conditions. The tests were repeated on the patients with elevated temperature when their temperature was normal, and no difference was noted.

Having decided that the drug was effective and safe if sensitivity were ruled out, it was then used on the following ten patients:

CASE REPORTS

CASE 1.—K. D. was a 2½-year-old white girl who had been operated on for ruptured appendix with peritonitis. Postoperatively she was given 0.02 mg. (20 μ g) hyaluronidase in the lateral aspect of each thigh, followed by 1,500 c.c. of normal saline. This was repeated for three days without changing the site of the needle. Through a misunderstanding, the needle was removed for four hours on the fourth day but later replaced in the same area and a clisis of 500 c.c. saline given on the fourth day and 1,500 c.c. of Ringer's solution and 2½ per cent glucose on the fifth day. The absorption was exceptionally good, and there was no evidence of any tissue reaction.

CASE 2.—A. H. was a 7-month-old infant with miliary tuberculosis, who was given 2,500 c.c. of 5 per cent glucose in saline over a period of five days, preceded by 20 μ g of hyaluronidase (0.2 c.c. of 100 μ g per cubic centimeter) in each thigh. The needles were left in the same place during this period, but after the third day there was inflammation of the tissue about the needle at the site of its insertion.

CASE 3.—M. C. was a 21-month-old female infant admitted for pneumonia with associated vomiting, diarrhea, and dehydration. She was given 200 c.c. of normal saline by clysis on two consecutive days, each one preceded by 20 μ g (0.2 c.c. of 100 μ g per cubic centimeter) of hyaluronidase. Absorption was satisfactory, and no discomfort to the patient was noted.

CASE 4.—F. B. was a 14-week-old infant who developed diarrhea. She was given 500 c.c. of 5 per cent glucose in saline into an area infiltrated with 20 μ g of hyaluronidase in the lateral aspect of the leg. This was repeated the next day in the same area without the use of additional hyaluronidase, and absorption was still satisfactory.

CASE 5.*—R. T. was a 3-week-old infant with pyloric stenosis. Three hundred cubic centimeters of 2½ per cent glucose in Hartman's solution were given on three successive days in the same area, preceded by 0.3 c.c. of 100 μ g per cubic centimeter of hyaluronidase. The rate of flow was adjusted to 8 to 12 drops per minute. On the first day, the solution ran for six and one-fourth hours, on the second day for four and three-fourths hours, and on the third day for five and one-fourth hours. At no time was there any elevation of the skin of the thighs at the site of the clysis.

CASE 6.*—M. B. was a newborn premature infant weighing 2½ pounds. One-tenth cubic centimeter of 100 μ g per cubic centimeter of hyaluronidase in 40 c.c. of 2½ per cent glucose in Hartman's solution was used on five occasions with steady absorption each time.

CASE 7.*—A. V. was a child with acute otitis media and a temperature of 104° F. Combined sulfadiazine and sulfamerazine were given subcutaneously and as the child was not taking fluids, a clysis of 500 c.c. of 2½ per cent glucose in Hartman's solution with 0.5 c.c. of 100 μ g per cubic centimeter of hyaluronidase was given. The clysis was completed in six hours. Only slight elevation of the skin of the thigh was noted.

CASE 8.—J. W. was a 6-week-old infant with diarrhea secondary to otitis media. He was given 200 c.c. of 5 per cent glucose in saline preceded by 20 μ g of hyaluronidase. The clysis was continued for five hours with no swelling or discomfort.

CASE 9.—S. C. was a 33-year-old woman who had had a hysterectomy. She was given a clysis of 1,000 c.c. of 5 per cent glucose at the rate of 100 drops per minute, and it was completed in three hours. Twenty micrograms of hyaluronidase (0.2 c.c. of 100 μ g per cubic centimeter) were given at the start of the clysis. There was slight swelling of the tissues after the clysis, but it was diffuse and not indurated.

CASE 10.—J. P. was a 33-year-old woman who had been operated on for a ruptured appendix. She was given 1,000 c.c. of 5 per cent glucose in water, preceded by 20 μ g of hyaluronidase. The clysis was completed in two and two-thirds hours, and there was slight swelling but no induration in the area.

DISCUSSION

Hyaluronidase was first described by Duran-Reynals⁵ and McClean⁶ as a spreading factor, but its identity as a mucolytic enzyme and its presence in all sources of the spreading factor was established by Chain and Duthie⁴ and confirmed by several others.⁷⁻⁹

*Patients studied at Flower-Fifth Avenue Hospitals.

This enzyme has been obtained from numerous sources, such as bacteria,^{4, 10-14} leech extracts,^{4, 15} bee, snake, and spider venoms,^{1, 16} spermatozoa,¹⁷⁻¹⁹ and mammalian testes.^{4, 20}

Its role in infection⁴ and fertilization²⁰⁻²² has been formulated, and more recently its role in fluid administration has been studied. In the present paper, the enzyme was studied from the latter point of view.

Enough of the hyaluronidase was given to several individuals to equal the amount that would be needed for the average elysis (20 μ g), and no harmful effects could be noted. In ten cases the hyaluronidase was repeated on three consecutive days, and no harmful effects on the urine were observed.

However, in testing skin sensitivity, 9.3 per cent of those tested had positive reactions, which suggests the advisability of skin testing each individual prior to administration of the enzyme. In fairness to the product, it must be added that it has not been completely purified, and perhaps the percentage of sensitivity can be reduced as more impurities are removed.

It was also noted that the addition of hyaluronidase to saline gave almost identical absorption times for all patients (healthy or ill, regardless), the difference being almost negligible, whereas in the Aldrich and McClure "saline test"²³ the rates of absorption were much more rapid in infectious diseases. This suggests⁴ that during illness there may be an increase of hyaluronidase formation by bacteria or possibly a decrease in hyaluronic acid formation in the tissue which increases the absorption of the saline.

The most important observation of all was that absorption of various types of solutions, such as saline, glucose in saline, Hartman's solution, Ringer's solution, penicillin, streptomycin, adrenalin, and procaine, was facilitated in every case.

In two of the patients elyses were run for five days, the needles remaining in the same area. It was noted that the tissue about the needle became inflamed after the third day; therefore it would be wise to change the site of the needle after that time.

Absorption was facilitated and pain diminished in every case. No consistent alterations in body physiology were detected.

SUMMARY AND CONCLUSION

1. Hyaluronidase had no harmful effect on any of the patients studied, although a positive intradermal skin test was obtained in 9.3 per cent.

2. The extent and duration of the pain and swelling associated with elysis were greatly reduced by use of the enzyme.

3. No alteration in body physiology was detected.

4. It greatly facilitated absorption of all solutions used.

5. The rate of absorption was practically identical for all patients, whether ill or not.

6. Continuous elysis for at least five days could be given, with the needle shifted after the third day.

7. It must be concluded that hyaluronidase proved of great value in the treatment of dehydrated infants. However, it would be of even greater value

were the product further purified so as to decrease the sensitivity factor. It is felt that hyaluronidase should be added to the medical armamentarium as a means of saving many children's lives.

Appreciation is gratefully expressed for the valuable assistance rendered in this study by Jack Hennessen and other members of the Senior Group of the New York Medical College and Flower-Fifth Avenue Hospitals.

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THE ORAL AND SUBCUTANEOUS ADMINISTRATION OF *p*-AMINOMETHYLBENZENESULFONAMIDE (SULFAMYLON)

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THE unique properties of *p*-aminomethylbenzenesulfonamide (*p*-(α -amino) toluenesulfonamide, homosulfanilamide, Marfanil, Sulfamylon*) have elicited considerable interest in its potentialities as a chemotherapeutic agent. It differs widely from other sulfonamides in certain important characteristics. In contrast to these compounds, Sulfamylon is freely soluble in water, to the extent of 50 Gm. per 100 ml. at 25° C. Its antibacterial action is in no way antagonized by either *p*-aminobenzoic acid or *p*-aminomethylbenzoic acid, and thus an entirely different mechanism of action is suggested.^{1, 2} Although Sulfamylon is effective against most organisms inhibited by other sulfonamides, it is, in addition, highly effective *in vitro* against a number of anaerobic bacteria, particularly clostridia.³

Sulfamylon was first utilized in Germany in the local treatment of various wound infections⁴ and subsequently specifically in the management of gas gangrene.⁵⁻⁸ More recently it has been applied to the systemic therapy of certain bacterial diseases, such as urinary tract infections, especially those resistant to other antibacterial agents.⁹ Recently a method for the quantitative determination of Sulfamylon in blood¹⁰ has been developed, making possible the present study on certain aspects of the pharmacology of this drug.

PLAN OF STUDY

The subjects were patients on the medical wards of the St. Louis Children's Hospital, who were for the most part convalescents free of gastrointestinal and renal disease. However, one patient with pyelonephritis and another with typhoid were included. The ages ranged from 7 months to 14 years.

Sulfamylon hydrochloride was given orally in the form of either 0.5 Gm. tablets or a 15 or 20 per cent solution in diluted (aqueous) syrup of cherry. A one per cent solution for subcutaneous administration was prepared by dilution of a Seitz-filtered 20 per cent aqueous solution of the hydrochloride with the appropriate volume of lactate Ringer's solution. At suitable intervals after single doses of the drug, blood samples were obtained and the concentration of Sulfamylon in the serum determined by the method previously described.¹⁰

From the Department of Pediatrics, Washington University School of Medicine, and the St. Louis Children's Hospital.

Much of this study was made possible through the aid of the Children's Research Foundation.

*Sulfamylon is the trade name of the product made by the Winthrop Chemical Company, New York, N. Y., which kindly supplied the material used in this study. For convenience, the name Sulfamylon will be used in place of *p*-aminomethylbenzenesulfonamide throughout this article.

All patients were observed closely for toxic manifestations, and all patients capable of reporting were questioned about toxic symptoms. Routine urinalyses and blood counts were carried out both before and after administration of the drug.

ORAL ADMINISTRATION

Included as subjects in this group were both infants and older children. A single dose of Sulfamylon hydrochloride was given to each subject, and the

SERUM LEVELS RESULTING FROM THE ORAL ADMINISTRATION OF SULFAMYLON 0.6 GM/KG

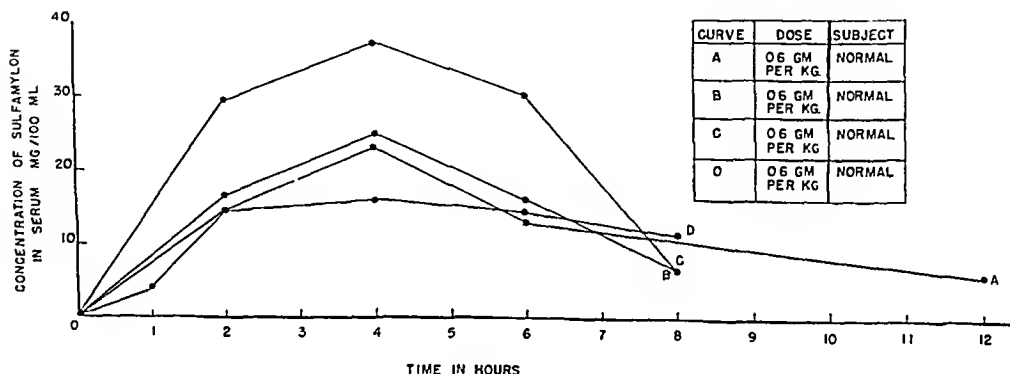


Fig. 1.

SERUM LEVELS FOLLOWING THE ORAL ADMINISTRATION OF SULFAMYLON

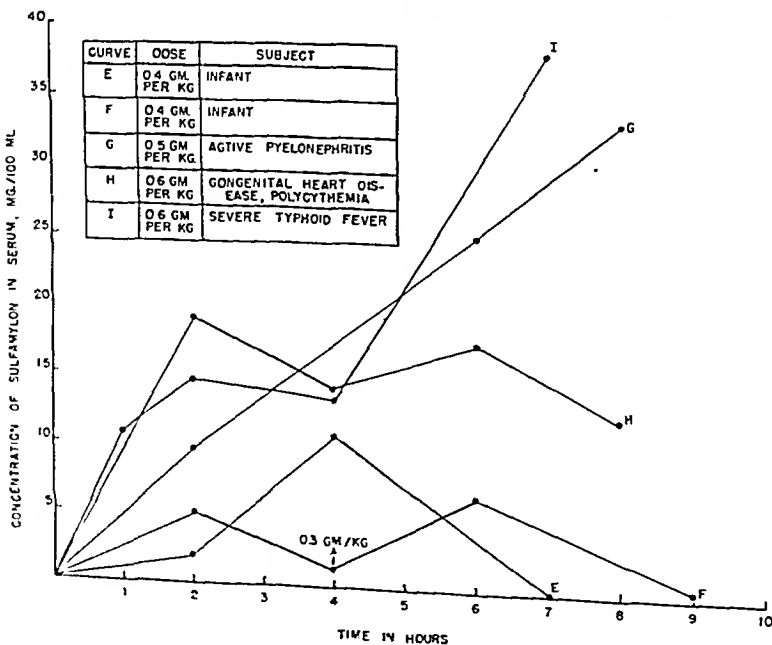


Fig. 2.

serum concentration of the drug was followed, usually by determination at two-hour intervals. The dosage ranged from 0.4 to 0.6 Gm. per kilogram of body weight. The observed data are presented in Figs. 1 and 2.

The most typical pattern is seen in the curves of Fig. 1. With a dosage of 0.6 Gm. per kilogram of body weight, there is a rise of the blood level to a peak approximately four hours after administration with subsequent rapid fall, so that by eight hours the serum level has returned to the vicinity of 10 mg. per 100 ml. or lower. Twenty-four hours after a single dose of 0.6 Gm. per kilogram of body weight there is no appreciable Sulfamylon remaining in the blood. Thus, fairly rapid absorption but rapid removal by excretion or destruction is indicated, and comparatively high dosage is needed to achieve the blood levels reported here. While dosage will obviously affect the drug concentrations obtained, individual differences in absorption evidently also effect considerable variation.

Comparison of all the curves presented in Figs. 1 and 2 demonstrates the wide variability in individual response to a single oral dose. The two infants reported in Curves E and F and two others studied with only one or two determinations achieved much lower blood levels than did children over 2 years of age on similar dosage, failing to attain serum concentrations higher than 10 mg. per 100 ml. at any time. Evidently the absorption of Sulfamylon from the immature digestive tract is relatively poor; similar phenomena have been observed upon oral administration of other sulfonamides.¹¹ In Fig. 2, Curve G's persistent rise can be explained on the basis of impaired excretion of the drug in the presence of pyelonephritis, while Curve I's delayed peak may be related to delayed absorption and impairment of renal function in a case of severe typhoid fever with cardiac failure. However, it is obvious that a wide variation in individual response may exist in the absence of any evident pathologic change to explain it. There are evidently marked individual differences in the ease with which Sulfamylon is absorbed from the alimentary canal, analogous to those observed in the case of other sulfonamides.

SUBCUTANEOUS ADMINISTRATION

All subjects receiving Sulfamylon by the subcutaneous route were convalescent patients, less than 2 years of age, without gastrointestinal or renal disease. A single infusion of one per cent Sulfamylon hydrochloride in lactate Ringer's solution was given, and serum levels of the drug were followed at one- or two-hour intervals. Dosage was either 0.5 Gm. or 0.6 Gm. per kilogram of body weight, except for one 0.3 Gm. per kilogram dose. The observed data are presented in Figs. 3 and 4.

Examination of these data reveals that all six curves adhere closely to a consistent pattern. The rise of Sulfamylon concentration in the serum is rapid but varies with the rate of infusion, and the peak level in every case comes very shortly after the end of the hypodermoclysis. This indicates that the absorption of Sulfamylon from subcutaneous fluid is very rapid. There is a rapid fall of drug concentration after the peak level is reached, so that again the blood level is generally near or below 10 mg. per 100 ml. within four hours after the peak.

SUBCUTANEOUS ADMINISTRATION OF SULFAMYLON

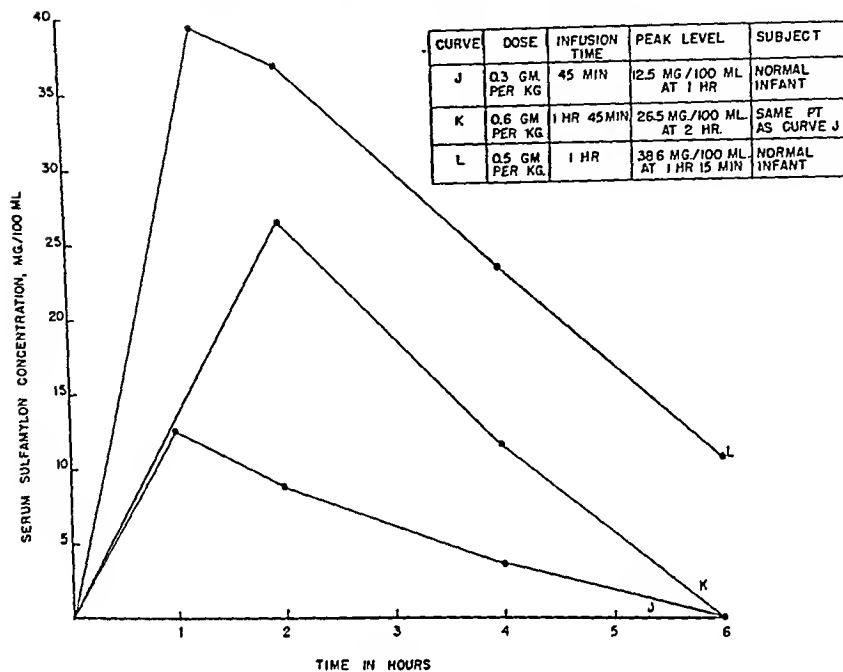


Fig. 3.

SUBCUTANEOUS ADMINISTRATION OF SULFAMYLON

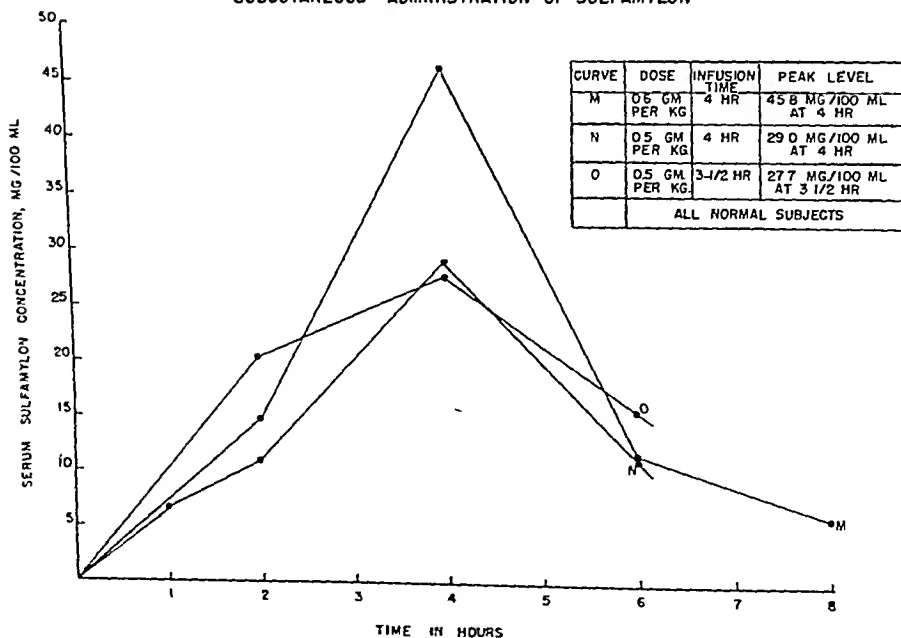


Fig. 1.

On the whole, blood levels obtained by the subcutaneous route are higher than those reached after oral administration of the same amount of Sulfamylon. In addition, the comparative uniformity of the response in different individuals receiving the drug subcutaneously is striking, and direct correlation of blood levels attained with the dosage received is observed, although there is some degree of individual variation. This adherence of curves obtained from subcutaneous administration to a nearly uniform pattern, as contrasted with the marked heterogeneity of the oral administration curves, confirms the idea that the variability shown in Figs. 1 and 2 is primarily in absorption, rather than excretion, in different individuals.

Upon comparison of the results of subcutaneous and oral administration it becomes evident that the subcutaneous route is indicated in children less than 2 years of age and offers a marked advantage in reproducibility in patients of any age. It obviously also presents a valuable method of administration in patients who are nauseated or vomiting, have gastrointestinal disease, or are severely ill.

NOTES ON MAINTENANCE OF THERAPEUTIC LEVELS

It may be inferred from the data presented that comparatively high dosage, similar to that utilized in these studies, repeated at fairly frequent intervals, is necessary to maintain serum levels at or above 10 mg. per 100 ml. Since clinical data indicating the approximate Sulfamylon levels necessary for effective treatment of various bacterial diseases have not yet been reported in the literature, no attempt will be made at present to recommend specific dosage schedules.

Certain additional observations are pertinent to the problem of maintaining therapeutic concentrations. Absorption after oral administration is variable but often quite adequate in patients above 2 years of age, while in infants it is very ineffective. More rapid attainment of a given blood level is obtained by subcutaneous administration, and in general it gives more reproducible results, Sulfamylon orally or absorb it well.

TOXICITY

All patients who received Sulfamylon hydrochloride orally and were capable of reporting their symptoms complained of nausea and headache, appearing shortly after the drug was taken. Three out of eleven subjects observed some dizziness, and two complained of mild mental confusion and slight dissociation. Two of the patients were sufficiently nauseated to vomit their first dose of the drug. All subjects receiving subcutaneous Sulfamylon were too young to communicate any untoward symptoms. Close observation of all patients receiving the single large oral or subcutaneous doses revealed no clinical signs of toxicity.

In view of the fact that the pH of a one per cent aqueous solution of Sulfamylon hydrochloride is 5.5, the drug was administered subcutaneously as one per cent Sulfamylon hydrochloride in lactate Ringer's solution; the pH of this preparation was 6.5. No local irritation or other signs of reaction at the site of injection were observed, and no pyrogenic or other systemic reactions

occurred. A 2 per cent solution of Sulfamylon in lactate Ringer's solution is equally free from side effects and provides a more convenient volume for infusion.

Sulfamylon hydrochloride is the salt of a strong acid and a weak base; hence its solutions are acidie. In the case of one patient maintained at high levels of Sulfamylon for twenty-three hours, acidosis developed. This girl, who was suffering from severe typhoid fever, received the following dosage of Sulfamylon hydrochloride: 0.6 Gm. per kilogram of body weight orally at 9:30 A.M.; 0.6 Gm. per kilogram orally at 3:30 P.M.; 0.55 Gm. per kilogram subcutaneously, as one per cent in lactate Ringer's solution, starting at 4:50 P.M.; 0.6 Gm. per kilogram orally at 8 P.M., 12 midnight, 4 A.M., and 8 A.M.; after this the drug was discontinued because of indications of resistance of the organism to Sulfamylon *in vitro*. At 4:30 P.M. the serum Sulfamylon level was 38 mg. per 100 ml., and at 8 A.M. it was 111 mg. per 100 ml. Hence we may assume that the serum level was above 30 mg. per 100 ml. for at least sixteen hours. At 8 A.M. the serum carbon dioxide content was found to be reduced to 29 volumes per cent. Upon simple discontinuance of the drug, without administration of additional base, acidosis was relieved spontaneously within eight hours, despite the massive concentration of Sulfamylon present at 8 A.M.

Routine urinalyses and blood counts were carried out upon all patients before and after administration of Sulfamylon. No abnormalities were shown in either. In particular, there were absolutely no laboratory or clinical signs of renal damage despite the high single doses. The patient with severe typhoid fever mentioned previously subsequently died and came to autopsy. There were no signs of toxic effects in the kidney, and no lesions in any part of the body that could be attributed to the drug. This is especially significant in view of the exceedingly high concentration of Sulfamylon maintained in this patient's blood. Additional evidence of the absence of renal damage was found in the fact that twenty-four hours after the serum level was found to be 111 mg. per 100 ml., it had dropped to less than 2 mg. per 100 ml.

SUMMARY

Single doses of Sulfamylon (hydrochloride) were administered to subjects and the blood levels followed at suitable intervals. Marked individual variations in absorption are evident after oral administration, with absorption apparently very poor in infants, while the data from subcutaneous administration present a relatively uniform picture. Sulfamylon is evidently excreted rapidly, and comparatively high dosage is required to attain appreciable concentrations in the blood serum.

Immediate toxic symptoms of headache and nausea were reported by all patients taking Sulfamylon orally, while dizziness and mental confusion were experienced by three. No local or systemic reactions were produced by the subcutaneous infusion of one per cent Sulfamylon hydrochloride in lactate Ringer's solution. No evidence of renal damage or hematopoietic depression was found either in routine urinalyses and blood counts on all patients or on post-mortem examination of one patient receiving very intensive Sulfamylon therapy for one day.

Grateful acknowledgment is made to Dr. Alexis F. Hartmann for advice and suggestions during the course of this work and in the preparation of this paper.

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GENERALIZED VACCINIA

A STUDY OF FIFTEEN CASES

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DURING the New York City smallpox outbreak of March, 1947, a well-known radio commentator made the following statement: "During this period there have been more deaths resulting from complications of vaccination than there have been deaths from smallpox." This true though very inept remark undoubtedly was misinterpreted by many listeners to be a condemnation of smallpox vaccination as a dangerous procedure.

The more pertinent facts that might have been revealed by the commentator include:

1. The incidence of smallpox¹ in the United States has been reduced as a result of an improved vaccination program from an average annual rate of 40,000 cases twenty years ago¹ to an average of less than 500 cases per annum during the years 1942 to 1947.²

2. By the prompt vaccination of more than six million individuals³ at the time of the New York outbreak, a potential smallpox epidemic was limited to a total of fourteen cases.⁴

3. Smallpox vaccination with fully potent vaccine, performed according to any one of the accepted methods, is with rare exceptions, a safe procedure.

It is proposed that if the severe vaccination complications can be further reduced to an absolute minimum, at least one of the obstacles impeding a nationwide compulsory vaccination program will have been removed.

Our study was made with the purpose of recalling to the attention of the general practitioner and the pediatrician the severe vaccination complication commonly known as generalized vaccinia. It is our belief that by careful attention of the vaccinating physician to a few prophylactic measures, the incidence of this condition will be markedly decreased.

In a recent report on certain aspects of the New York smallpox outbreak and subsequent mass vaccination, Muekenfuss⁵ stated that thirty-six cases of generalized vaccinia are known to have occurred. Twenty-two of the persons so affected had not themselves been vaccinated. Our series consists of fifteen of these thirty-six individuals who manifested generalized vaccinal lesions. These patients were admitted to the Willard Parker Hospital for Contagious Diseases in April and May, 1947.

The patients with generalized vaccinia whom we observed were acutely and distressingly ill. This was especially true of the infants and young children in whom multiple vaccinal lesions were superimposed upon an atopic eczema. Rather complete clinical and laboratory studies were made on each of the fifteen

¹From the Willard Parker Hospital for Contagious Diseases, Department of Hospitals, New York City.

patients, but since to report every case in detail would be repetitious, only four are described. These case reports, together with the data in Table I and the subsequent discussion, will present the outstanding characteristics of generalized vaccinia as observed in this series.

CASE REPORTS

CASE 1.—This was a Negro male infant, 3 months of age, admitted to the hospital May 7, 1947. The history indicated that the child had suffered from eczema of the face and scalp since the age of one month.

According to the parent's statement, the sequence of events immediately preceding the child's admission to the hospital was as follows: The mother was vaccinated against smallpox April 14, with a resulting primary vaccinia which reached its height on April 23. Ten days later the infant (who had not been vaccinated against smallpox) developed pustular vesicles on the face. Shortly afterward similar lesions appeared on the scalp, upper extremities, trunk, and legs, and four days later the infant was so ill as to necessitate hospital care.



Fig. 1.—Patient in Case 1. Photograph taken on the fifth day of illness.

When this infant was admitted to the hospital, he was acutely ill and semicomatose. The temperature was 105° F., the pulse and respirations extremely rapid. Masses of confluent crusted lesions, from some of which pus oozed, were on the face. The right eyelid was closed by extensive involvement of that area, but there was no corneal lesion. Lesions on the scalp, anterior trunk, and extremities were present, though more discrete and of varying stages. One pustule was present on the right palm, but there was no involvement of the mucous membranes. The typical individual lesion was a slightly raised, flat pustule, 5 to 7 mm. in diameter, at first umbilicated, later crusted.

High fever and extreme prostration continued for the first four days of hospitalization, with daily elevations of temperature to 104° and 105° F. Thereafter the temperature fell by lysis and remained normal after the tenth hospital day. By the end of the first week of hospitalization (eleven days after onset) the individual skin lesions were desquamating and forming new crusts. The areas where lesions had previously conalesced on the face became raw and weeping. After eleven days in the hospital the lesions on the

body were fairly well cleared, and the skin of the face and extremities was assuming an eczematoid character. The lesions of the right eyelid had subsided, and the eye itself was normal.

Routine urinalysis was negative. Admission cultures of the lesions were positive for *Staphylococcus aureus* and *Bacillus proteus*. Hemoglobin was 63 per cent, with a red blood cell count of 4 million. The white blood cell count was 13,100, with neutrophils 56 per cent, lymphocytes 35 per cent, myelocytes 2 per cent, metamyelocytes 2 per cent, monocytes 2 per cent, eosinophiles 3 per cent. The Paul test was positive, and vaccinia virus was recovered on chorio-allantoic culture.

Treatment consisted of penicillin, 10,000 units given intramuscularly every three hours, prevention of self-traumatization by the combination of methods to be described under Treatment, penicillin ointment applied locally to the lesions, and hot compresses used for the palpebral edema. A soybean milk substitute was given, and known or suspected allergens were eliminated from the diet.

On subsidence of the acute illness and of the vaccinia lesions, local treatment was instituted for the underlying eczema, and on the thirtieth hospital day the patient was discharged. At that time the face and upper extremities were moderately scarred. Follow-up two weeks after discharge revealed depigmentation without pitting of the areas previously involved by the vaccinia lesions.

CASE 2.—The patient was an 8-month-old white male infant admitted to Willard Parker Hospital May 16, 1947, because of high fever and a generalized pustular eruption. The history included typical infantile eczema with onset at the age of 3 weeks followed by alternate periods of improvement and exacerbation.

When the infant was 6 months old the mother inquired of the family doctor concerning smallpox vaccination and was advised against the procedure because of the presence of infantile eczema. Consequently the patient had never been vaccinated. However, approximately two weeks before the admission date both parents were vaccinated and developed what apparently were accelerated reactions.

On examination of the infant on May 11, there were noted by the family doctor confluent vesicular lesions on the left side of the face. In the four days preceding admission these lesions extended to involve all parts of the body except the posterior aspect of the trunk, the genitalia, the soles of the feet, and the right palm.

Examination on admission to the hospital revealed a desperately ill male infant with a temperature of 103° F., and scratching the involved areas of skin with both hands and feet. An umbilicated pustular eruption was present, the lesions being confluent in the left cervical region and left cheek and discrete on the right side of the face, the anterior surface of the trunk, and the extremities. Three lesions were noted on the left palm.

The typical discrete lesion was firm, pustular, and umbilicated, measuring about 0.5 cm. in diameter. Some lesions were mounted on an erythematous base. Not all lesions had developed this characteristic umbilicated appearance, while others had advanced to the crusting stage. Areas of excoriation in which the skin had apparently been completely denuded by scratching were present on the arms, legs, and chest.

There was noted a generalized lymphadenopathy with most marked enlargement of the axillary and inguinal glands. The largest of these glands measured about 2 cm. in diameter. Skin turgor on admission was poor.

The red cell count was 4.34 million, and the hemoglobin was 13 Gm. or 90 per cent of normal. The total white count was 12,800, with 85 per cent polymorphonuclear cells and 15 per cent lymphocytes. Total serum protein was 5.1 Gm. per cent, of which albumin constituted 3.2 Gm. per cent and globulin 1.9 Gm. per cent. The Paul test was negative. Material from the lesions showed a type of growth characteristic of vaccinia virus on the chorio-allantoic culture.

The infant's temperature rose to 103° F. on the second and third hospital days. The extremities became spastic, nystagmus developed, and the skin turgor was only slightly improved. The skin lesions were observed to progress rather rapidly through the umbilicated stage to the crusted stage.

A soybean formula was taken fairly well by mouth, while plasma was given intravenously and normal saline was given by elysis. Aspirin and tepid sponges on uninvolved surfaces were used in an attempt to control fever. Penicillin was administered intramuscularly, and penicillin ointment was applied locally.

The infant failed to respond to treatment. Fever, spasticity, and nystagmus persisted, and death occurred on the fourth hospital day.

Post-mortem examination revealed an extensive crusting pustular eruption involving particularly the cheeks, forehead, arms, and legs, with a few lesions noted on the left palm. Microscopic examination of a typical skin lesion revealed a superficial flat vesicle covered with coagulated epithelium and filled with some cellular debris, along with polymorphonuclear cells and groups of cocci. Areas of mononuclear infiltration were noted in the subjacent corium. The brain appeared quite pale, and the meninges were slightly edematous. The weight of the brain was 830 Gm., and sectioning showed no significant congestion. Microscopic examination of various parts of the brain showed mononuclear infiltration of the walls of numerous small veins in the white matter and also in the gray matter. The brain substance showed no cellular infiltration around the affected blood vessels, and there was no appreciable loss of myelin. Section of the lumbar cord showed infiltration of the walls of several small veins in the posterior horns, posterior white column, and in the gray commissure.

The anatomical diagnosis was: (1) generalized vaccinia, (2) chronic eczema, (3) encephalomyelitis without loss of myelin.*

CASE 3.—The patient was a 9-month-old Negro male infant who was admitted to Willard Parker Hospital April 27, 1947, because of fever and a skin eruption of twenty-four hours' duration. The infant had infantile eczema at the age of 5 months, but two months before admission there had been a marked improvement in this condition following the substitution for milk of a soybean preparation.

Because of the eczema the infant had not been vaccinated against smallpox. However the parents were vaccinated on April 17, nine days before the onset of the patient's eruption. Both parents developed primary reactions, and shortly thereafter there were noted what were described as pustular lesions about the lobe of the infant's left ear. These lesions were quite pruritic as evidenced by the fact that they were scratched so vigorously as to leave a denuded area.

By the day of admission, pustular lesions had appeared on the right shoulder and extremities. On admission, physical examination revealed an acutely ill, lethargic child. The temperature was 104° F., and the pulse and respirations were correspondingly rapid.

The skin of the face and the left ear was densely covered with umbilicated or crusted raised pustular lesions, some of which were coalescent with denuded weeping patches. The trunk and the extremities, including the dorsum of the hands and feet, were involved by similar lesions, but the mucous membranes and the palms and soles were not involved. Portions of the skin, clear of lesions, were thickened and bore numerous superficial scratch marks. There was a generalized lymphadenopathy with marked involvement of the cervical, posterior auricular, axillary, and inguinal nodes. The remainder of the physical examination was not significant.

Routine urinalysis on admission revealed four-plus albumin. No casts or red cells were observed. The carbon dioxide combining power was 43 volumes per cent. The N.P.N. was 24 mg. per cent. Total serum protein was 6.4 Gm. with an A/G ratio of 1.3 to 1. The hemoglobin was 9 Gm., with a red blood cell count of 4 million. The white blood cell count was 12,000, with a normal differential. A blood culture was negative. The serologic test for syphilis was negative. Inoculation of penicillin-treated material, from the lesion to the chorio-allantoic membrane of embryonated eggs, showed a characteristic

*A detailed discussion of this case and of other cases of encephalitis which occurred in New York during the same period will be made by Dolgopel, Greenberg, and Arnoff at a later date.

growth of the vaccinia virus. The Paul test was unsatisfactory. Bone marrow studies performed on material obtained from sternal puncture were within normal limits.

For seven days after admission there were diurnal rises of temperature ranging between 103.8° and 105.4° F. The temperature returned to normal on the tenth hospital day, but there were subsequent elevations to 102° and 105° F. on the sixteenth and twenty-seventh hospital days, respectively.

The lesions appeared in successive crops over the body, with pustular, weeping, and crusted lesions often all present in close proximity. Pustules appearing subsequent to the first crop were observed to mature more rapidly than the initial lesions. With the return of the temperature to normal, on the tenth hospital day, the lesions began to subside and form innocuous-appearing crusts. By the eighteenth hospital day, there was generalized desquamation of the crusts, leaving a severe pruritic eczema. The albuminuria gradually subsided and was no longer observed after one month. Treatment consisted of parenteral and local penicillin, restraints, and a soybean milk formula. Benadryl failed to give any observable alleviation of itching in this case.

The infant was discharged on the forty-second hospital day, with recommendations for further treatment of the eczema at a dermatology clinic. The degree of scarring of the face on discharge was difficult to evaluate because of the eczema which persisted.

CASE 4.—This patient was a 28-month-old white male infant admitted to the hospital April 27, 1947, following vaccination in the left deltoid region on April 17. There was a history of severe and persistent atopic eczema present since early infancy. Benadryl had been used with some temporary improvement of the eczema. Known allergens included citrus fruits, egg, wheat, and chocolate. The only other pertinent fact obtained from the history was a sensitivity of the father to pollens and dusts.

Three days following vaccination there developed marked pruritis in the left deltoid region, which was scratched vigorously by the patient. Small red papular lesions appeared about the vaccination site, and seven days after vaccination the eruption spread to involve the posterior cervical region. At this stage the child appeared acutely ill, became restless and irritable, and the family doctor administered a sedative along with local antipruritics. Further extension of the lesions followed with involvement of all body surfaces except the palms, soles, and mucous membranes.

Physical examination on admission revealed an acutely ill, though well-nourished and well-developed 28-month-old boy with a temperature of 103° F. Firm pustular umbilicated lesions with an erythematous base were noted on the face, neck, trunk, and extremities. The majority of the lesions were umbilicated or weeping, while some were crusted. A few lesions, though pustular in character, appeared to be topped by small vesicles. The conjunctivae and pharynx were injected, and there was a mucopurulent discharge from the eyes and nose. The cervical and left axillary glands were enlarged.

Routine urinalysis showed a trace of albumin and occasional pus cells. The white blood cell count was 11,000 with 50 per cent polymorphonuclears, 46 per cent lymphocytes, 2 per cent eosinophiles, and 2 per cent metamyelocytes. The characteristic vaccinia virus growth was obtained upon inoculation of material from the lesions on the special chorio-allantoic culture medium. The Paul test was unsatisfactory. Examination of the sternal marrow revealed no abnormalities.* The Kline test was positive.

The most marked involvement as noted on the second hospital day was of the arms, the suprascapular and posterior cervical regions, and the popliteal fossae. A few lesions were also noted on the eyelids. At this time the eruption was definitely polymorphous. Some lesions were deep-seated, erythematous papules, some were weeping, umbilicated pustules, and still others were crusted.

Treatment consisted of the use of penicillin intramuscularly and locally, sedation, and aspirin as an antipyretic. Restraint constituted a major problem in this case. The combination of methods found to be most efficacious is described in detail under *Treatment*.

*Bone marrow studies in this series were performed by Dr. Thomas Louis Rider of the Willard Parker Hospital house staff.

Response to therapy was satisfactory, the temperature remaining normal after the ninth hospital day, and the patient was discharged on the fourteenth day of hospitalization.

Follow-up examination three weeks after discharge revealed erythematous scaly areas where the vaccinia lesions had been located. No pitting was observed.



Fig. 2.—Patient in Case 6. Photograph taken three days after admission. Note different stages of lesions on cheek and forehead.

DIAGNOSIS

Incidence.—One seldom sees a series of cases of generalized vaccinia unless a large number of persons have been vaccinated against smallpox. There is, however, some indication that virus of unusual potency may be a factor in producing this condition. The most recent report on generalized vaccinia is from Clark and his associates.⁶ They estimate an incidence of one case of generalized vaccinia to 13,390 vaccinations. Ross,⁷ on the basis of data accumulated by a number of European authors, suggests the incidence as being one in twenty to forty thousand cases of routine vaccination. It is quite likely, however, that this condition is not as rare as statistics would indicate, as mild attacks probably seldom come under medical observation and even when they do are seldom reported. The statistical frequency of generalized vaccinia may well be decreased, too, by the fact that an occasional case is undoubtedly misdiagnosed as variola, impetigo, or secondarily infected varicella.

In the New York experience, with an estimated six million vaccinations, only thirty-six cases of generalized vaccinia came to light. But inasmuch as twenty-two of these patients had not themselves been vaccinated, and because most patients with generalized vaccinia manifest an underlying chronic dermatosis, it would appear not entirely safe to establish an incidence rate by utilizing only discovered cases of generalized vaccinia as the numerator and the number of persons vaccinated against smallpox as the denominator. Attack rates of

generalized vaccinia appear to depend more upon exposure of persons with eczema to vaccine virus than upon the number of persons vaccinated, and it is not practicable to obtain data of this sort. The fifteen patients whom we studied constitute too small a number to yield any data as to incidence of generalized vaccinia by age, sex, or race. Eleven of the patients were Negro, as against four white patients, while the ratio in New York City of white persons to Negroes is about fourteen to one. However the comparative number of white and Negro eczema patients exposed to vaccine virus is not known. Probably, too, economic circumstances brought a greater proportion of Negro than white patients to the Willard Parker Hospital. There were eleven males and four females, and ages ranged from 13 months to 64 years, with a majority of the cases in infants. (See Table I.) It is suggestive, however, that the predominance of males and infants is similar to the distribution of atopic eczema in the general population.

Eight of the fifteen patients had not themselves been vaccinated against smallpox, but the unvaccinated group had been exposed to recently vaccinated members of their respective families. In less than half of this group was there history of direct contact with the vaccination area of another individual.

It is believed that generalized vaccinia does occur more frequently in individuals exhibiting a primary vaccination reaction. All vaccinated individuals in our series had been vaccinated for the first time.

Period of Incubation.—All information upon which the period of incubation of generalized vaccinia might be calculated was obtained from parents and therefore may not be relied upon with confidence. In seven of our patients vaccinated conventionally, the time from date of the vaccination to the manifestation of the first evidence of multiple vaccinia lesions ranged from one to seven days with a mean of 4.5 days. In the series as a whole, including patients for whom data were obviously unreliable, the range was from one to twenty days, with a mean of eleven days and a median of nine days. Perhaps in cases where the patient was not himself vaccinated, it would be more nearly exact to date exposure as of the day that vaccination in the source contact reached pustular stage rather than as of the date vaccination was performed. Other observers estimate the incubation period as seven to ten days. In this connection, it is to be noted that lesions arising after the first crop tend to mature more quickly than do the original lesions.

Contributing Factors.—Eleven of our patients gave a history of infantile atopic eczema. One patient receiving antisyphilitic therapy had an arsenical dermatitis. Two others had concurrent dermatoses, eczemoid in character but not specifically classified, while in the last patient the vaccinia was superimposed on variella. Nimpfer⁸ reported four cases of generalized vaccinia lesions in patients suffering from burns, thus adding another group highly susceptible to vaccinia virus. Parenthetically, it is interesting here to note that several hundred patients with variella were vaccinated against smallpox, in the usual manner, at Willard Parker Hospital, and so far as is known only one developed generalized vaccinia lesions.

Diagnosis.—The clinical diagnosis of generalized vaccinia lesions was usually made without difficulty. All case histories included some concurrent skin

disease, a recent smallpox vaccination either in the patient or his close contacts, and a negative history for exposure to variola. The presence of multiple, pustular umbilicated lesions, asymmetrically distributed, associated with pruritis, toxicity, and fever, completed prerequisites for clinical diagnosis. Subsequent immune reaction to smallpox vaccination in children never before vaccinated may also be considered significant.

Laboratory tests, while most useful in the hands of experienced technicians, are not usually available, and the final diagnosis in most cases must rest upon the clinical findings. The diagnostic methods of choice are the Paul test, the complement fixation test, and the neutralization test. A fourth method as developed by Hirst⁹ consists in identification by growth characteristics on the chorio-allantoic membrane of eggs. The virus of smallpox, obtained from persons with active cases of the disease who were in the hospital at the time, produced a growth pattern which was easily differentiated from that of the vaccinia virus.

A modification of the Paul test in this series was helpful, although in five cases there were negative or unsatisfactory results. The modified Paul test was performed by inoculating a rabbit's cornea with the crusted material from a vaccinia lesion. Upon the development of a definite gross keratitis, sections of the tissue were examined microscopically for Guarnieri bodies. Complete bone marrow studies on five patients in this series failed to reveal any characteristic abnormalities.

Differential Diagnosis.—In the differential diagnosis, one must consider impetigo, variola, erythema multiforme bullosa, postvaccinal urticarial reactions, and multiple vaccination (complications of vaccination which we observed). Other diseases that may be confused with generalized vaccinia include herpes zoster and pustular syphilis.

In impetigo, the lesions are seldom umbilicated and fever is not a usual accompaniment. Variola may occur within the first five to six days after a vaccination, and diagnosis in most cases must rest upon history and clinical manifestations. There was seldom a history of prodromata in the patients with generalized vaccinia whom we observed, while the eruption of variola is characteristically preceded by headache, backache, and malaise. The early lesions of a generalized vaccinal infection are full-blown umbilicated vesicles, while those of variola are firm, salmon-pink nodules, which only later develop frank vesiculation. We observed no cases of generalized vaccinia lesions on the mucous membranes, a typical site for variola lesions. Continuation of fever after the appearance of the eruption occurs regularly in generalized vaccinia though not in variola. Erythema multiforme bullosa and urticaria-like lesions may occur following vaccination, but these conditions are not easily confused with generalized vaccinia. Multiple vaccination is characterized by autoinoculation of only one or two lesions, usually on the face or hands. Herpes zoster typically follows a nerve trunk and is very painful, thus enabling differentiation from vaccinal lesions, which have no predilection for nerve trunks and appear to cause only a pruritis. Pustular syphilis can usually be definitely diagnosed by history and serologic tests.

Course of the Disease.—The onset, as mentioned previously, was not accompanied by the rather severe prodromata characteristic of variola. The first manifestation, in most cases, was the appearance of multiple lesions, either about the vaccination site or elsewhere, followed by fever, prostration, and regional lymphadenopathy. The course was, in most cases, remarkably rapid, especially in those who contracted the virus from the vaccination of close contacts. The two fatalities observed in the series occurred in infants who had never been vaccinated.

In most cases there was a rapid spread and progression of the lesions on the second day of illness. The temperature frequently reached 105° F., and prostration was severe at this time. From the second to the seventh days of the illness, successive crops of lesions erupted over different areas of the body. There was a definite affinity for eezematoid tissue, but skin which had previously appeared healthy was involved also to a lesser extent. In only four instances were there lesions on the palms and soles, and in none of the cases were lesions present on the mucous membranes. The temperature of the less severely affected patients usually had subsided to normal by the fifth or sixth day of illness. In some of the more critically ill patients the temperature persisted as high as 104° F. until the eighth or tenth day. Toxicity ran closely parallel to the fever in its severity. With the fall in temperature, the appetite increased and the patient appeared to be in far better spirits.

The lesions, in the early stages, were umbilicated pustules. These frequently coalesced to form a mat of pustules, which soon broke down to leave a denuded, weeping area. This was frequently noted over the more severely affected eezematoid areas. The individual lesion was, on the average, from 6 to 10 mm. in diameter. In the isolated lesion a mild erythematous areola could be seen, but this was not comparable to that seen in the usual solitary reaction following intentional vaccination.

The umbilicated pustular form persisted for six to twelve days, when the lesion became rather heavily crusted and slightly larger than the original. This stage lasted for a variable period, desquamating and leaving an atrophic pale pink maculé of corresponding size. Eezematoid tissue, where there was a confluence of the lesions, tended to be scarred, while the individual lesion left a barely perceptible blemish. Follow-up of vaccinia cases occurring in Negro patients showed considerable loss of pigment in the more severely involved areas.

Dissemination of Virus.—Ellis¹⁰ felt that the cutaneous distribution in eezema vaccinatum was due to hematogenous spread. Tedder¹¹ believes that true generalized vaccinia is "a disturbance (following vaccination) of the balance between virus and the virucidal substances which it calls forth in a person having an intact healthy skin, so that the virus which is disseminated hematogenously becomes active in the skin, producing a generalized vesicopustular eruption, lesions on the mucosa and general symptoms." He adds: "Eezema vaccinatum in most instances represents inoculation even when the eruption is widely spread over the body."

It is now generally accepted that in an uncomplicated smallpox vaccination the virus is disseminated throughout the body by the circulation (Gins,¹²

Paschen,¹³ Jubb,¹⁴ Leake,¹⁵ and others). Thus one must assume that in generalized vaccinia, whether or not contributed to by an underlying eczema, there is a hematogenous dissemination of the virus throughout the body. If, in atopic eczema, the multiple lesions arise by hematogenous spread, then it must be presupposed that the portions of the skin affected by eczema are areas of lowered resistance to blood stream implantation of the virus. Against this hypothesis is the fact that when multiple vaccinia lesions occur in those persons themselves vaccinated, they tend to appear first, but not invariably, as a satellite crop around the vaccination and later appear in eczemoid areas. Hematogenous spread of the vaccinia virus results in the presence of the virus in the nose and throat secretions of individuals vaccinated four to five days previously. This probably accounts for the cases of generalized vaccinia in those who are unvaccinated and have not had known direct contact with the vaccination area of another individual.

Clark,⁶ in commenting upon three cases in the Edinburgh series, which three he designated as "heterogenous vaccinia," states that "the cases had certain features in common—(a) the children were all under 5 years of age, (b) none of them had ever been vaccinated, (c) all were having ointment inunected for concurrent skin disorders, and (d) other members of the household were having vaccinia reactions dressed." Subsequently, in these three patients, vaccinia lesions appeared in the areas inunected.

Treatment.—Our experience with generalized vaccinia lesions leads us to suggest the following treatment:

1. The suppression and prevention of secondary infection by the use of parenteral penicillin and saline compresses or penicillin ointment locally as indicated.

2. The prevention of further allergic reactions by removing from the diet the usual allergenic foods, including milk, orange juice, chocolate, wheat, and egg.

3. The prevention of further autoinoculation through restraint of infants from scratching. This was best accomplished by the following combination of methods: (a) The patient was placed in such a position as to minimize friction between the bed and the most extensively involved area. (b) Elbow splints were applied. (c) Fingernails and toenails were clipped short, and the hands were covered with white cotton stockings. (d) The involved areas were further protected by the application of protective dressings with penicillin ointment. (e) An eczema jacket may be used, but it is believed that no effort should be made toward body immobilization because of the danger of hypostatic pneumonia or respiratory obstruction from aspirated vomitus.

4. The maintenance of adequate hydration and of the proper balance of the body electrolytes was of course important, particularly in the infants with extensive involvement.

NOMENCLATURE AND CLASSIFICATION

Cases of generalized vaccinia lesions have received a number of different designations, and as a result the multiplicity of synonyms is confusing. Ron-

chese¹⁶ lists the following: Kaposi's varicelliform eruption, pustulosis vaccini-formis acuta (Freund), eezema vaccinatum, pustulosis acuta varioliformis (Juliusberg), postvaccinial eruption, generalized vaccinia (Venturi), eezema varicellatum (or variolatum), and eezema herpetiforme. Ronchese, himself, used the term dermatitis vaccinia. Because many of these terms were employed at a time when there was little knowledge of bacteriology and no knowledge of viruses, description rather than etiology was the primary consideration. For this reason, it cannot be said that the individual lesions in each case, described by these various titles, contained the virus of vaccinia or that they were produced by only one etiological agent.

In recent years, the confusing nomenclature has been partially clarified by the elimination of several synonymous terms, but enough are still in common usage to create misunderstanding. While others are occasionally employed, the three designations generally accepted for the presence of multiple lesions of vaccinia are: Kaposi's varicelliform eruption, eezema vaccinatum, and generalized vaccinia.

The first of these, Kaposi's varicelliform eruption, is a descriptive term which has been applied to any eruption resembling varicella (or vaccinia) when it occurs on an eezematous child. The etiology has been ascribed to a host of organisms, including the streptococcus, the virus of herpes simplex, and the virus of vaccinia. Kaposi himself appears to have felt that the causative agent might be a fungus.

The inclusion of manifestations of several distinct and separate organisms under one diagnosis was probably justified in 1887 when Kaposi described his "alarming complication of eezema." But although the lesions of the herpes virus, the streptococcus, and vaccinia on or in the skin of an eezematous infant may exhibit superficial similarity, it must be remembered that each of these infecting agents produces different systemic and local reactions, so that under the Kaposi designation any one of at least three pathologic conditions might be involved. The significance and preciseness of such a term as "Kaposi's varicelliform eruption" is open to question. There is some logical objection, too, to utilization of the word "varicelliform" in a condition that is not varicella or any modification of it, but is, in fact, vaccinia. Such a designation is not only confusing from the standpoint of etiological understanding, but is misleading even as a descriptive term.

In the circumstances, and for the sake of clarity, it would seem appropriate to consider etiology rather than gross appearance as a basis for nomenclature in this instance, and when the virus of vaccinia is present, to use the term "generalized vaccinia."

A second cause of confusion in terminology seems to have arisen from the assumption that in those cases where multiple lesions of vaccinia appear upon a healthy skin, the spread was hematogenous from the initial lesion of vaccinia; and that when similar multiple vaccinial lesions occur in a person with eezema (whether the initial lesion of vaccinia was caused purposely or accidentally) the spread was by a series of individual surface implantations. Apparently, some observers have tended to base terminology upon this assumed pathogenesis and

TABLE I. SUMMARY DESCRIPTION OF FIFTY-N PATIENTS WITH GENERALIZED VACCINIA OBSERVED AT WHIT AND PALMER HOSPITAL, FOR CONTAGIOUS DISEASES IN THE PERIOD APRIL-JUNE, 1917

CASE NO.	AGE	SEX	RACE	VACCINATION OR EXPOSURE TO VACCINATION	INCUBATION PERIOD* (DAYS)	DISTRIBUTION OF GENERALIZED VACCINIA LESIONS	UNDERLYING SKIN CONDITION	WHIT-BLOOD COUNTS (THOUSANDS)	LABORATORY FINDINGS			OUTCOME
									SYPHILIS SEROLOGIC	PAT. L. LIQUE	RECOVERY OF VACCINIAL VIRUS†	
1	3 mo.	M	N	Mother vaccinated 1/14	19	Face, scalp, arms, trunk, legs, 1 on palm	Atopic eczema	13.1	Neg.	Pos.	Pos.	Recov.
2	8 mo.	M	W	Parents vaccinated 5/2	14	Over all of body, not on soles, 3 on left palm	Atopic eczema	12.8	Neg.	Neg.	Pos.	Died
3	9 mo.	M	N	Mother vaccinated 1/17	9	Head, face, shoulders, neck, dorsum, feet	Atopic eczema	12.0	Neg.	+	Pos.	Recov.
4	28 mo.	M	W	Own vaccination 1/17	6	Back, neck, shoulders, extremities	Atopic eczema	11.0	Pos.	+	Pos.	Recov.
5	6 mo.	M	N	Mother vaccinated 4/20	11	Head, scalp, arms, legs	Atopic eczema	11.5	Neg.	Not done	Pos.	Recov.
6	11 mo.	M	N	Brother vaccinated 4/19	20	Face, hand, thigh	Atopic eczema	10.0	Neg.	Pos.	Pos.	Recov.
7	13 wk.	F	N	Mother vaccinated 4/23	8	Face, scalp	Atopic eczema	15.8	Neg.	Pos.	Pos.	Recov.
8	4 mo.	F	W	Family vaccinated 4/17	19	Face, arms, legs, palm	Atopic eczema		Neg.	Pos.	Pos.	Died
9	58 yr.	M	N	Vaccinated 4/18	2	Face, arms, legs, neck, trunk	Chronic eczema; cause?		Neg.	Pos.	Pos.	Recov.
10	2 yr.	M	N	Vaccinated 4/14	2(?)	Right arm, right shoulder, and right upper thorax	Atopic eczema	12.7	Neg.	Not done	Pos.	Recov.
11	12 yr.	M	N	Vaccinated 4/13	7	Right arm and forearm	Arseus dermatitis	11.6	Pos.	+	Pos.	Recov.
12	64 yr.	F	N	Vaccinated 4/9	6	Arms, legs, few on trunk	Eczema; cause?	10.3	Neg.	Pos.	Pos.	Recov.
13	2 yr.	F	W	2 brothers, parents vaccinated 5/10	16	Face, popliteal, right groin, elbow	Atopic eczema	24.5	Neg.	Pos.	Pos.	Recov.
14	3 1/2 yr.	M	W	Own vaccination 4/18	6	Face, arms, popliteal	Chronic atopic eczema	14.2	Neg.	Pos.	Pos.	Recov.
15	6 yr.	M	N	Vaccinated 4/19	6	Chest, abdomen	Varicella	Not determined		+	Pos.	Recov.

*Calculated from informant's statements †Chorio-allantoic membrane, embryonated egg. ‡Unsatisfactory.

would thus limit use of the term "generalized vaccinia" to the appearance of multiple lesions of vaccinia on a skin healthy and intact other than for the initial vaccinia lesion, and to designate as *eczema vaccinatum* only those cases in which multiple lesions appear on an individual with *eczema*. But even if the mode of dissemination constituted a sound base for nosology, it has not been demonstrated that multiple vaccinia lesions in a healthy skin arise only through hematogenous spread or that those on an *eczemoid* base are never similarly spread. Actually, of course, the virus of vaccinia has repeatedly been shown to be present in the blood stream, and once the virus is introduced, either purposely or accidentally in a child with *eczema* or with a healthy skin, the spread could be either hematogenous or by external autoinoculation. Regardless of the manner of spread of the virus, multiple lesions of vaccinia in persons with *eczema* and in those without differ only from the standpoint of susceptibility of the skin: In both instances, generalized vaccinia is present. Even though the underlying *eczema* may predispose to generalization of vaccinia, *eczema* and vaccination are separate conditions, and it would not seem justifiable to employ a designation such as *eczema vaccinatum*, which would suggest that together they constitute a third entity.

In view of these various considerations, generalized vaccinia is perhaps the generic term of choice, whether or not the condition is complicated by *eczema*.

CONCLUSIONS

1. Fifteen cases of generalized vaccinia are reported with recommendation for treatment.

2. Patients with *eczema* and burns should not be vaccinated, nor should they remain in the same household with those recently vaccinated.

3. Postvaccination complications in atopic *eczema* strongly suggest the advisability of vaccination during the first few months of life before the onset of most allergic skin conditions and before the acquisition by the infant of "scratchability."

4. It is important that every individual being vaccinated against smallpox be questioned concerning active *eczematous* conditions in himself or in members of his household. In the presence of the first condition the vaccination should be postponed until subsidence of the *eczema*. In the presence of *eczema* in a member of the household, the vaccinated individual should live apart from the *eczematous* individual until completion of the vaccination reaction.

5. "Kaposi's varicelliform eruption" should be regarded only as a descriptive term and not as a clinical entity. The term should not be employed when etiology has been established. Generalized vaccinia is the term of choice.

We are indebted to Dr. George K. Hirst, Chief of the Division of Infectious Diseases, Public Health Research Institute of New York, for his work on vaccinia cultures, and to Dr. Vera Dolgopel, pathologist of the Willard Parker Hospital staff, for reports on the Paul test.

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A CASE HISTORY OF BREAST FEEDING SUCCESSFULLY
ESTABLISHED DURING THE THIRD POST-PARTUM
WEEK ON A SELF-REGULATING FEEDING
PROGRAM

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FEW questions are of more practical or theoretical importance for the physical and psychological welfare of the mother and her newborn baby than the question of breast feeding. Yet, despite the importance of the question, scientific information concerning the prognosis for successful breast feeding is meager, although many theories concerning the reasons for the low incidence of successful breast feeding in our society have been advanced. Because of our meager information regarding the prognosis for breast feeding, the following case of the successful establishment of breast feeding after the fifteenth post-partum day is worthy of study. Before turning to a discussion of the case, a brief review of some of the available research is indicated.

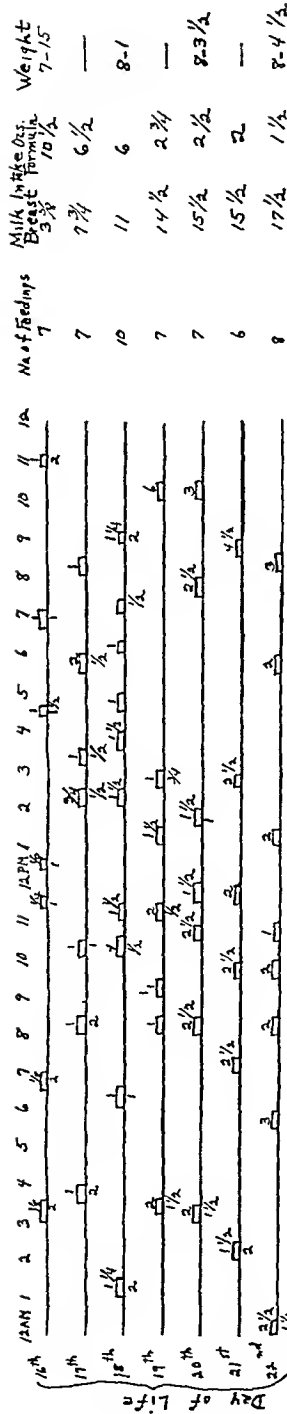
REVIEW OF RESEARCH

Mead¹ has reported that among the Mundugumor of New Guinea some adoptive mothers who have never borne infants or who have not suckled a child for many years can develop a secretion of breast milk under the stimulating effect of a child's sucking combined with drinking large quantities of coconut milk. Stewart and Pratt² in a study of 900 successive cases of breast feeding found that no case of deficient lactation increased to full breast nursing by the tenth postpartum day. They have, however, presented data which suggest that the suckling stimulus may account for the higher incidence of full breast nursing among primiparas who place their babies early on both breasts.³ Selye⁴ has demonstrated the important role of the suckling stimulus in the lactation of normal animals.

FEEDING HISTORY OF CHILD M

Early Feeding History.—Child M, a normal infant weighing 8 pounds, 1 ounce, was delivered by cesarean section. Although the mother was eager to breast feed her infant, her condition following delivery made it impossible to initiate breast feedings until the fifth post-partum day. From the fifth through the fifteenth day of the infant's life he was offered breast feedings five and later six times daily in accordance with usual hospital practice. In addition he received supplementary feedings. During this hospital period, the infant never received more than one ounce of breast milk at any feeding. His nursings at the breast lacked vigor and he often fell asleep early in the nursing period.

*Mother of the infant.



Key:
□ Feeding
Above □ intake of breast milk
Below □ intake of formula milk

Chart 1.—Behavior day chart, first week of self-regulating feedings.

Initiation of Self-Regulating Feedings.—Scheduled feedings were abandoned on the fifteenth day when the mother and baby returned from the hospital. Detailed feeding records were commenced on the sixteenth day of the infant's life, the first full day of self-regulating feedings. During this early period at home supplementary bottle feedings were given immediately following the breast feeding and an effort was made to keep the feedings as small as possible with the aim of having the infant sufficiently hungry to nurse vigorously at the breast. The program was undertaken under the guidance of a pediatrician and with the aid of a pediatric nurse. As the infant became launched upon this program the mother soon observed marked differences in the nursing behavior. The infant nursed at the breast more vigorously and for longer periods, some of the nursings lasting for one-half hour or longer.

Feeding History During the First Week of Self-Regulating Feedings.—Chart 1 plots the feeding history during this first week of self-regulating feedings, from the sixteenth through the twenty-second days of life, and shows the approximate amounts of intake of breast and bottle milk. The total intake of $3\frac{5}{8}$ oz. of breast milk on the sixteenth day of life with an intake of only $\frac{1}{8}$ oz. at three of the feedings confirms the hospital feeding history of an almost negligible amount of breast milk intake. As Chart 1 shows, the total daily intake of breast milk increased during this week to $17\frac{1}{2}$ oz. in eight feedings during the twenty-second day of life. This increase in breast milk intake was accompanied by a decrease in the amount of formula milk taken. On the sixteenth day the infant took a total of $10\frac{1}{2}$ oz. of formula milk, but on the twenty-second day he took only $1\frac{1}{2}$ oz. During this week, as the chart shows, the infant gained $5\frac{1}{2}$ oz. He took a total of fifty-two feedings, a number considerably in excess of the six daily feedings that had been planned for him during the hospital period.

Feeding History from the Twenty-third Through the Fifty-eighth Day of Life.—Chart 2 shows the number of daily feedings from the sixteenth through the fifty-eighth day of life, the amount of intake of breast or formula milk and the amount of weight gain. Following the twenty-second day, the mother maintained a supply of breast milk adequate, or nearly adequate, to meet the infant's apparent needs. One or very occasionally two complementary bottle feedings were given each day commencing with the twenty-sixth day of life. These complementary feedings were often given in lieu of the early morning breast feeding in order that the mother might have a longer uninterrupted sleep. Occasional supplementary bottle feedings were given. During the week from the forty-fourth to the fifty-first day of life the mother secreted on the average about $22\frac{1}{2}$ oz. of breast milk each day. Thus breast feeding had been successfully established.

Spontaneous Scheduling.—Child M, like other self-regulating infants who have been studied spontaneously, reduced the number of his daily feedings but it is notable that it was not until the eighth week of life that he took as few as thirty-six feedings during the week. Also like other self-regulating infants whose feeding histories have been recorded, he showed a marked tendency to

take his longest sleep after his late afternoon feeding or occasionally even after a midafternoon feeding. On his forty-third day of life he slept from 6:30 P.M. until 1:00 A.M. On four days during the following two-week period he slept for intervals of approximately ten hours, commencing these sleeping periods about 6 to 7 P.M. On his fifty-eighth day of life he slept from 2:00 P.M. to 1:00 A.M.

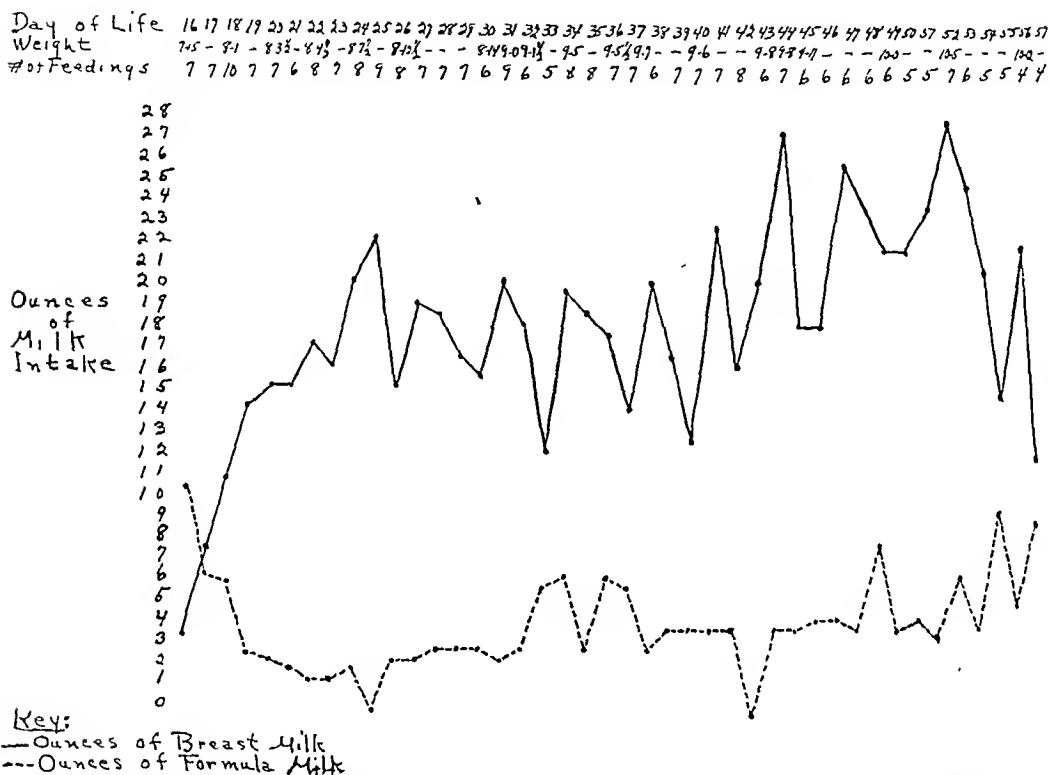


Chart. 2.—Daily intake of breast and formula milk, weight gain, and number of daily feedings, sixteenth through fifty-seventh day of life.

COMPARISON WITH OTHER SELF-REGULATION INFANTS

Child M's feeding picture is so similar in certain aspects to the feeding picture in the case of the two infants studied by Simsarian and McLendon³ that comparisons seem appropriate. All three infants took more than fifty feedings during a week in the early weeks of self-regulating feedings and as many as ten and eleven daily feedings on some days during the early period of adjustment. All three protracted their nursings for thirty minutes or longer at some feedings, particularly during the early period. This tendency to protract some nursings was also observed in twin infants studied by Trainham et al.⁷ However, these latter infants took few feedings, never more than thirty-five feedings during a single week. Unquestionably as more and more children on self-regulating schedules are studied we will gain new insights into some of the ways in which different parental handling as well as other factors may affect the feeding picture.

SUMMARY AND EVALUATION

The mother's intense desire to nurse her infant is attested to by her eagerness to continue nursing even in the face of what appeared to be an unfavorable prognosis at the time when mother and baby left the hospital. The mother derived such pleasure from nursing the infant that she felt more than amply rewarded for the unusual efforts which she had made.

A mother who produced only a negligible amount of breast milk for her infant during the fifteen days of hospitalization was able to produce a supply of breast milk adequate, or nearly adequate, to meet her infant's needs during the first week at home when the infant was placed on a self-regulating schedule. The infant took a total of fifty-two feedings during this week increasing the daily amount of breast milk taken from $3\frac{5}{8}$ oz. on the sixteenth day to $17\frac{1}{2}$ oz. on the twenty-second day. Similarities to other case histories of self-regulating feeding have been noted.

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PERTUSSIS IN INFANCY

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WHOOPING cough is no doubt the most devastating acute infectious disease of infancy, exacting its heaviest toll particularly during the first year of life. When the current incidence and mortality are viewed historically, it may appear that whooping cough has become a mild disease, but the fact still remains that it poses one of the severest hazards to the life of the infant. Sauer¹ and Lapin² have repeatedly written that pertussis is an extremely serious disease during infancy. Davis and Carroll³ have recently studied the mortality from whooping cough in Texas. In 1943 there were one-third more deaths attributable to whooping cough than to diphtheria, measles, and scarlet fever combined for all age groups. In children under the age of one year, whooping cough caused nearly seven times as many deaths as the other three diseases combined.

CLINICAL MATERIAL

The present study is an analysis of 137 patients under the age of 2 years admitted to The Infants' and Children's Hospitals in Boston between 1931 and 1945 with a diagnosis of whooping cough. Of this group, forty-five were treated with pertussis hyperimmune serum,* or a globulin concentrate derived from hyperimmune human serum† after admission to the hospital. Since pertussis hyperimmune serum was not used at The Infants' and Children's Hospitals prior to January, 1941, patients admitted before that date are included as a background for comparison with the serum-treated group. A subsequent follow-up study is planned in order to observe the long-term effects of this disease when it occurs in the first two years of life. No evaluation of serum therapy is possible unless the two groups are comparable as regards the severity of the disease before institution of specific therapy.

In order to compare the severity of disease in the serum-treated group with that in the group not receiving serum we have listed in Tables I through VII certain statistical findings applicable to both groups of patients. In these tables the group receiving serum after admission is called Group A, and the one which did not receive serum is Group B.

1. *Age and Sex.*—The age and sex distributions of the patients studied, divided into two groups according to whether serum was used in treatment, are presented in Table I.

According to Table I the average age of the patients in Group A was two and one-half months younger than that of the patients in Group B. There was

From The Infants' and Children's Hospitals, Boston.

*Distributed by the Serum Exchange, Philadelphia Children's Hospital.

†Concentrated human hyperimmune pertussis globulin (Hypertussis) was prepared and kindly supplied by the Cutter Laboratories of Berkeley, Calif.

TABLE I. AGE AND SEX DISTRIBUTION

AGE IN MONTHS	GROUP A		GROUP B	
	BOYS	GIRLS	BOYS	GIRLS
22-24	0	0	3	1
19-21	0	1	2	2
16-18	0	0	3	3
13-15	1	1	2	5
10-12	1	3	3	5
7-9	6	3	9	6
4-6	7	2	3	17
1-3	10	10	17	15
Totals	25	20	38	54
	Total Number	45		92
	Average Age	5.9 months		8.5 months

no attempt to select cases. All critically ill patients admitted after hyperimmune serum became available received this therapeutic agent.

2. *Duration of Disease Prior to Hospital Admission.*—In estimating the length of time during which the disease was present prior to hospital entry, the onset of cough was taken as the beginning of the disease, since this sign is more reliable than such signs as malaise, irritability, restlessness, or coryza. In Table II there is presented a distribution of the intervals during which coughing was present before hospital admission.

TABLE II. DURATION OF DISEASE BEFORE HOSPITAL ADMISSION

DAYS	GROUP A	GROUP B
60-69	0	1
50-59	0	0
40-49	0	2
30-39	1	5
20-29	8	23
10-19	20	28
0-9	16	33
Total	45	92
Average	13.7 days	16.2 days

As a rule, patients were not referred to the hospital unless more alarming signs and symptoms than coughing were present. It was usually these additional signs and symptoms which were responsible for the eventual admission of the patient.

3. *Signs and Symptoms.*—In Table III there are listed the signs and symptoms present in the patients at the time of hospital admission.

The cough of pertussis differs from other coughs observed in infancy chiefly because of its paroxysmal nature, each coughing outburst initiating in trigger

TABLE III. FREQUENCY OF SIGNS AND SYMPTOMS ON ADMISSION

SIGNS AND SYMPTOMS	GROUP A		GROUP B	
	NUMBER	PER CENT	NUMBER	PER CENT
Paroxysmal cough	45	100	92	100
Vomiting	31	70	66	72
Cyanosis	20	67	51	55
Whoop	17	20	30	33
Convulsive episodes	10	22	16	17
Anorexia	7	16	17	18

fashion a series of coughing reflexes of progressive intensity. In the absence of paroxysmal coughing, observed in every patient studied, the clinical diagnosis of pertussis cannot be made safely.

Next in frequency was vomiting, observed in 70 per cent of the patients and occurring at the end of, or in the midst of, a coughing paroxysm and not usually present as a sign independent of the cough. Anorexia did not seem to accompany vomiting, and as can be seen from Table III, it occurred rather infrequently.

Cyanosis occurred with distressing frequency, particularly among the younger patients. The inspiratory crow, termed the "whoop," was present in only about one-third of the patients.

Convulsive episodes, which could not be attributed to other causes, occurred more frequently in the patients of Group A. Both clonic and tonic movements were observed, rolling back of the eyes, staring, and apparent loss of consciousness. In one patient, convulsive movements were present continuously from the moment of admission to her death several hours later.

4. *Laboratory Data.*—Laboratory procedures were usually limited to routine blood counts and bacterial cultures by means of cough plates and nasopharyngeal swabs. The degree of leucocytosis is listed in Table IV. Each blood count represented in Table IV was the highest count obtained during the patient's hospital treatment.

TABLE IV. DEGREE OF LEUCOCYTOSIS (HIGHEST WHITE BLOOD COUNT OBTAINED DURING HOSPITALIZATION)

WBC (THOUSANDS)	GROUP A	GROUP B
130 and above	1	1
110—129	0	1
90—109	0	2
70—89	2	4
50—69	4	8
30—49	16	20
20 and below	22	52
Number	45	88
Average WBC	(No WBC reported on four patients) 37.3 thousands	34.3 thousands

The degree of lymphocytosis varied from 40 to 90 per cent, the majority of blood smears showing 60 to 80 per cent lymphocytes. A predominance of lymphocytes was present in approximately 75 per cent of the smears.

From our records it appears that the bacteriologic diagnosis of pertussis is a difficult procedure. Until recently the most common practice was to hold an open Bordet-Gengou (B.G.) plate before a coughing patient, a technique which has not proved satisfactory. In 1942, Brooks and his associates⁴ described the advantages of their nasopharyngeal culture over the traditional cough plate culture in obtaining bacteriologic evidence of whooping cough infection. Silverthorne and his co-workers⁵ have found that a direct smear of nasal mucus produced 80 per cent positives in showing gram-negative bacilli. Cough plate cul-

tures in their series gave 55 per cent positives. In Table V are listed the results of cultures of B.G. cough plates and of nasopharyngeal swabs.

TABLE V. CULTURES OF B.G. PLATES AND NASOPHARYNGEAL SWABS

	GROUP A		GROUP B	
	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE
B.G. cough plate	1	6	4	25
Culture of nasopharyngeal swab	13	22	1	40

In the remainder of the patients either no attempt was made at bacteriologic diagnosis or contamination of cultures occurred. These figures probably serve only to show that the handling of pertussis cultures in a routine hospital laboratory is not satisfactory. The low incidence of positive cultures for the patients in Group B, most of whom were admitted prior to 1941, merely serves to show that in the absence of specific therapy less pains are apt to be taken to make an accurate laboratory diagnosis. When special care is taken by a trained technician in obtaining and culturing the organisms, as has been done recently, a much higher percentage of positive cultures is obtained.

5. *Complications.*—In Table VI are listed the complications encountered in the present series of cases and their relative frequency. These complications were present when the patients were admitted.

TABLE VI. FREQUENCY OF COMPLICATIONS IN PERTUSSIS AT TIME OF ADMISSION

COMPLICATION	GROUP A		GROUP B	
	NUMBER	PER CENT	NUMBER	PER CENT
Pneumonia	22	46	47	51
Bronchitis	6	13	13	14
Otitis media:	12	25	18	20
Nonsuppurative	(7)		(5)	
Suppurative	(5)		(13)	
Encephalopathy	7	15	12	13
Atelectasis	2	4	2	2
Emphysema	1	2	3	3
Nutritional disturbances	2	4	5	5
Umbilical hernia	1	2	4	4

The most frequent complication, and also the most serious, was pneumonia, present in approximately 50 per cent of the patients. According to the roentgenographic descriptions, the pneumonic process was usually interstitial or peribronchial in type. Until the advent of sulfonamides the mortality from this complication was appallingly high.⁶ For the purpose of this study a diagnosis of pneumonia was not tabulated unless there was x-ray evidence of a pneumonic process. In the absence of this confirmatory evidence, but when the breath sounds were altered in character, when there was an acceleration of respiratory rate, and when respiratory distress was apparent, a diagnosis of bronchitis was made. It is felt that in these patients the differences between pneumonia and bronchitis were probably quantitative rather than qualitative.

The next most frequent complication was otitis media, both the nonsuppurative and suppurative types occurring. In Group A twelve cases occurred, whereas in the other group eighteen cases were observed.

There were nineteen cases of encephalopathy, seven in Group A and twelve in Group B. Convulsive seizures were observed in all nineteen patients. From the standpoint of prognosis, convulsive seizures were a bad sign since every patient who eventually died exhibited this sign early in his hospital course.

Atelectasis, emphysema, umbilical hernia, and nutritional disturbance each occurred in 5 per cent of the patients, or less, as shown in Table VI. A diagnosis of nutritional disturbance was made when there was persistent diarrhea with attending loss of weight and dehydration, although food intake was not necessarily diminished.

TABLE VII. DATA ON EXPOSURE

HISTORY OF EXPOSURE	NUMBER OF CASES
Intimate exposure to member of same family at home	69
Casual exposure in neighborhood or in same apartment	26
No known exposure	42

6. *Data on Exposure.*—In 69 patients accurate and satisfactory data on exposure were obtained. In these cases there was at least one sibling at home with signs and symptoms of the acute stage of pertussis which would account for the patient's exposure. In twenty-six additional patients the history of exposures was less definite, being in the nature of a casual contact with a coughing person living in the immediate neighborhood. In the remaining forty-two patients no history of exposure was obtained, although in all cases such a history was sought.

7. *Patients With a History of Pertussis Prophylaxis.*—In seven patients there was a history of prophylactic injections of pertussis antigen, but in five of these the procedure could not be considered adequate. One patient had completed a series of three injections of Sauer's vaccine three months before the onset of symptoms. This patient, a girl aged 18 months, was casually exposed to a child with whooping cough. She required only eight days of hospital care, chiefly because of the co-existence of a suppurative left otitis media and pneumonia. Her course was uneventful and she made a good recovery. In only one other patient was there a history of adequate prophylaxis. This was in a boy, aged 9 months, who had been admitted to the neurological ward with a diagnosis of chronic subdural hematoma one month after completing a series of three pertussis antigen injections. Exposure could not be satisfactorily determined. His course was rather uneventful.

Another of our patients was a 19-month-old girl who had received two injections of Sauer's vaccine, one at the age of 8 months, the second injection at 14 months. This was certainly not an acceptable method of immunizing against pertussis. Four other patients received subcutaneous pertussis antigen injections after the onset of symptoms, a procedure of no value whatsoever.

In our series no patient who received adequate prophylaxis and subsequently contracted whooping cough exhibited convulsive phenomena or showed evidence of a severe infection. We have been unable to find any recorded case in which a patient who had received adequate prophylaxis succumbed to pertussis or its complications.

In summary, the cases of pertussis observed in this hospital were quite severe, with a high incidence of complications, and the findings were typical of the classical descriptions of the disease in infancy. Cultural proof of the diagnosis was not obtained in most cases. Although serum has been used in treatment only since 1941 and for only the severer cases, a comparison of the serum-treated group with the group receiving no serum indicates that the two groups were very similar with respect to the various indices of severity, although the average age of the former group was somewhat lower than that of the latter group.

TREATMENT OF ACTIVE PERTUSSIS

1. *Convalescent Blood, Blood Derivatives, Sulfonamides, and Penicillin.*—Within recent years three new therapeutic agents have been employed in the treatment of active pertussis and its complications, exclusive of the supportive measures which have, no doubt, contributed to the speeding up of convalescence and to the lowering of mortality. These agents are pertussis hyperimmune serum and the sulfonamides and penicillin, usually employed in treating a complicating pneumonia or other secondary infections known to be sensitive to these two chemotherapeutic agents. From a review of the literature, it can be seen that many materials have been employed in treating whooping cough, but very few agents have withstood the test of time.

Cohen, Weichsel, and Lapin,⁷ in a comparative study of Sauer's vaccine, typhoid vaccine, saline solution, convalescent serum, and hyperimmune serum used to treat active whooping cough, concluded that the first three agents had

TABLE VIII. HYPERIMMUNE SERUM IN THE TREATMENT OF WHOOPING COUGH

INVESTIGATOR	NUMBER OF CASES	NUMBER OF DEATHS	COMMENTS
McGuiness, Stokes, Mudd ¹²	15	0	Small dosage employed. One-third showed much improvement
McGuiness, Bradford, Armstrong ¹³	100	3	51 patients, 6 months of age and under. Results very good
Frank, Patton, Hamilton ⁶	30	6	2½ to 3 c.c. of serum per pound of body weight. All patients had bronchopneumonia complicating pertussis; 20 per cent mortality
McGuiness, Stokes, Armstrong ¹⁴	315	5	Mortality rate of 1.5 per cent. Excellent or good results in nearly 70 per cent
Scheinblum, Bullova ¹⁸	23	2	Sulfadiazine also given patients with pneumonia. Good results in 52 per cent, moderately good in 26 per cent
McGuiness, Armstrong, Pelton ¹⁵	442	6	55 of this group known to have pneumonia. Only ten patients received sulfonamides. Results on the whole excellent
Lapin ¹⁶	25	6	Tenfold globulin concentrate of human serum employed. Marked or moderate improvement in 70 per cent
Kohn and his associates ¹⁷	201	4	152 received human serum; 49 received rabbit serum; 2 per cent mortality

no merit but found that the two blood derivatives were of some value. The work of Silverthorne and Brown⁸ with immune rabbit serum, and that of Bustamente and Zozoya⁹ with immune goat serum would seem to indicate that both of these products are of value in prophylaxis and treatment but, to be sure, are not as practical or safe as homologous hyperimmune serum.

In 1935 Bradford¹⁰ published a historical survey on the use of convalescent blood and blood derivatives in the treatment of active pertussis, concluding that convalescent serum or immune whole blood, if given before the onset of catarrhal symptoms, possessed protective qualities. In 1937 Meader¹¹ reported that 10 c.c. of pooled convalescent blood protected 67.8 per cent of 115 exposed children, whereas only 34 per cent of a comparable group of 183 exposed controls avoided developing pertussis. In Table VIII appears a summary of studies in which hyperimmune serum has been used to treat cases of active pertussis.

Felton¹² and Ewers²⁰ have recently reviewed the serum therapy of pertussis and concluded that it has definite value. Although the evidence in favor of serum is suggestive, the difficulty of establishing clear-cut criteria for evaluation, the general decline in mortality from pertussis and other infectious diseases, and the lack of alternate case controls in these studies prevent their being considered conclusive.

2. *Supportive Measures.*—Before presenting the results of the treatment of forty-five patients in our series with pertussis hyperimmune serum, we shall mention some of the more useful supportive measures which have been employed.

The restoration and maintenance of fluid and electrolyte balance are of paramount importance. Accordingly, intravenous saline and glucose were administered routinely to those patients whose state of hydration had been seriously altered. When it was found that serum proteins were diminished, casein hydrolysate and blood plasma were administered. Occasionally transfusions of whole blood have been given.

Sedation has nearly always been used. Phenobarbital, nembutal, paraldehyde, ether in olive oil per rectum, and cough syrups containing codeine have been employed frequently. In critically ill patients, oxygen therapy has been found of great value in diminishing cyanosis, while aspiration of the nasopharynx and oropharynx has lessened the number of choking episodes and apnea. Certain water-soluble vitamin preparations have been administered orally or parenterally. Peroral oily preparations should be avoided, owing to the hazard of lipoid pneumonia.

3. *Treatment in the Present Series.*—The patients are classified into four groups according to the therapy they received. In seventy-one patients therapy consisted of supportive measures exclusively; in twelve patients treatment consisted of sulfonamides plus supportive therapy; twenty-nine patients received sulfonamides, serum, and supportive therapy; the remaining sixteen patients were given serum and supportive treatment. After 1937 sulfonamides were administered to all patients in whom a diagnosis of pneumonia was made, or in whom there was an intercurrent infection known to respond to sulfonamides. In the patients who received pertussis hyperimmune serum the dosage paralleled

closely that recommended by McGuinness and his associates,¹³ although in twenty-six patients the amount was below 60 c.e. (40 to 50 c.e.); nineteen patients received amounts between 70 and 100 c.e.

Clinically it has been found significant to follow the weight of infant patients in evaluating the progress of any disease as well as the effectiveness of its treatment. It is also a well-recognized fact that the weight of infants will vary markedly during the course of many diseases. In our patients this was true. In Table IX there are listed data on weight gain and weight loss during the period of hospitalization.

TABLE IX. WEIGHT GAIN AND LOSS DURING HOSPITALIZATION

WEIGHT RESPONSE	SERUM-TREATED	NO SERUM
Gained	25	38
Lost	10	25
No change	10	11

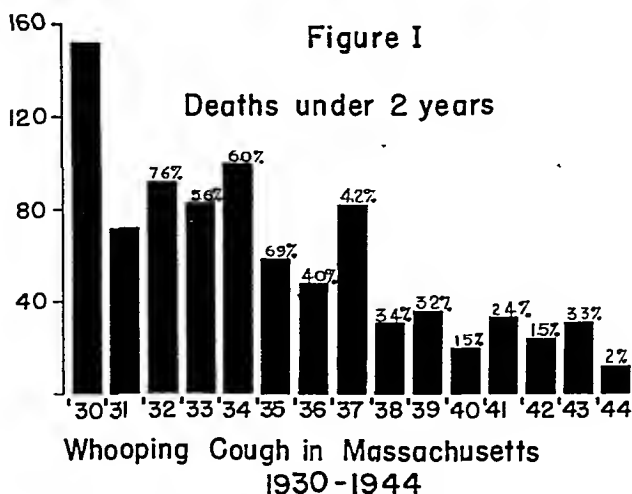
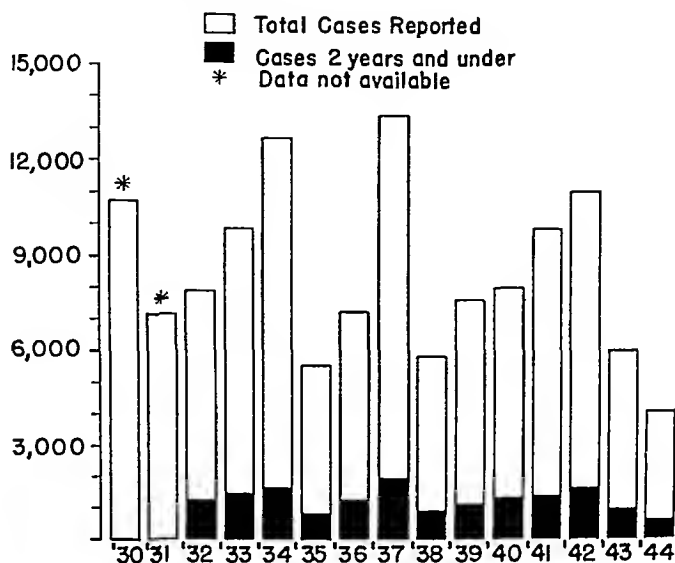
Upon being discharged from the hospital, sixty-three patients showed a gain over the admission weight, and thirty-five showed a weight loss. From Table IX it can be seen that there was no significant difference in terms of weight gain or loss in the two groups.

The patients who died were all in critical condition at the time of admission to the hospital. One patient, aged 4 months, showed signs of a severe encephalopathy upon admission, with increased pressure and 89 mg. per cent of total protein on lumbar puncture. She had had severe episodes of coughing at home for ten days prior to admission; her course was steadily downhill, and she died on the fourth hospital day. Post-mortem smears of the trachea for bacteria showed many *Hemophilus pertussis* organisms. Another patient was admitted at the age of 5 months. She had been coughing severely at home for approximately two weeks, having many episodes of cyanosis, and had been unable to retain food for ten days. Upon admission she was moribund, failed to respond to resuscitative measures, and died a few hours later.

In 1938 a 2-month-old girl was admitted with a three-week history of cough, cyanosis, and convulsive twitching. Her right upper lobe showed pneumonic consolidation. She failed to respond to all treatment and died six hours after admission. Another infant, aged 3 months, was admitted with a three-week history of paroxysmal cough, cyanosis, vomiting, and marked weight loss. The parents stated that the child had lost 5 pounds during this period of time. Upon admission this baby showed x-ray evidence of pneumonia and the clinical signs of meningism and marasmus. She lived for three days, receiving parenteral feedings and being maintained in an oxygen tent at all times. At autopsy, Type 29 pneumococci were recovered from her upper bronchi.

The most recent death from whooping cough occurred in a baby girl admitted in November, 1943, at the age of 14 months. She had been coughing rather violently for three weeks. Two older siblings at home had been coughing just as severely as the patient. However when the patient began to exhibit severe cyanosis and generalized convulsive movements, she was brought to the

hospital where the following diagnoses were made: pertussis, bilateral pneumonia, bilateral nonsuppurative otitis media, and encephalitis. Her temperature upon admission was 105° F. rectally, and it was noted in the clinical records that she was almost constantly in a convulsive state. She seemed to improve following a lumbar puncture, but then her temperature began to rise, finally reaching 108° F., whereupon she went into a continuous convulsive state and died seven hours after admission.



Five of the nine deaths reported occurred during the first hospital day, two patients died during their second hospital day, one during the third, and one during the fourth. In this series of cases, if a patient were alive for three or four days following hospitalization, recovery was the rule.

The effectiveness of serum therapy cannot, at least in this series, be judged by the effect on case fatality rate alone, because it is our impression that in recent years pertussis has not been as serious a disease as previously. As can be seen from Fig. 1, which has been adapted from the Vital Statistics for the Commonwealth of Massachusetts, the number of deaths attributable to whooping cough has diminished markedly since 1930. Unfortunately, data for 1930 and 1931 on the number of cases in children under 2 years of age were not available. The percentages over the solid bars in the lower half of Fig. 1 refer to fatality rates based on the number of cases reported for children 2 years of age and under.* The fatality rate fell sharply to its average present level between 1935 and 1940.

The decline in mortality observed during the past fifteen years is probably due to a number of factors. In addition to the possibility that the disease is not as severe as it was previously, the introduction of sulfonamides with their effect in lowering the mortality attributable to complicating pneumonia, and the increasing popularity of pertussis immunization are to be considered. Supportive therapy has improved considerably, especially in the restoration and maintenance of fluid and electrolyte balance in vomiting patients.

TABLE X. FATALITY IN PRESENT SERIES

	SERUM-TREATED	NO SERUM			TOTAL FOR ALL CASES
	1941-1945	1932-1941	1941-1945	TOTAL	
No. of cases	45	67	25	92	137
No. of deaths	1	7	1	8	9
Per cent	2.2	10.4	4.0	8.7	6.6

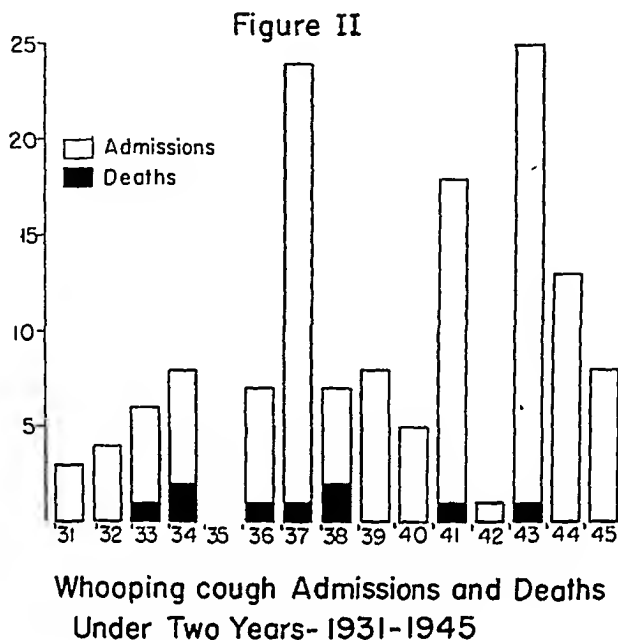
In the present series of cases nine deaths occurred. One death occurred among the serum-treated group and eight in the other group. It is interesting to note that seven of the deaths in the group not treated with hyperimmune serum occurred prior to 1941. A total of twenty-five patients was treated after 1941 with agents other than pertussis hyperimmune serum, and in this group the fatality rate was 4 per cent. During the years under review the observed fatality rate of 6.6 per cent may appear unduly high, but it must be kept in mind that this rate applies only to hospital patients, and ordinarily infants with pertussis are not brought to the hospital unless they are critically ill.

No attempt has been made in this study to correlate the type of therapy with actual duration of the disease. The length of the period of hospitalization was apparently influenced by the severity of the disease upon admission rather than by the type of therapy employed.

There has been a marked annual variation in the number of cases coming to The Infants' and Children's Hospitals for admission and in the number of deaths occurring during the years under review. (See Fig. 2.) In this series no deaths occurred after 1943, and only two deaths occurred between 1939 and 1945—that is, two deaths out of seventy-eight patients admitted during this interval.

*These percentages are actually of doubtful significance, because cases of whooping cough are generally very inadequately reported.

4. *Streptomycin*.—The effect of streptomycin in experimental pertussis in animals has been studied by Bradford and Day²¹ and by Hegarty and his associates.²² According to their preliminary reports, streptomycin should prove to be an extremely valuable drug in the treatment of clinical pertussis and is now being compared with serum therapy in this hospital.



NEUROLOGICAL AND PSYCHOLOGICAL CONSIDERATIONS

Ellison²³ has summarized existing theories of the pathologic physiology of convulsive phenomena occurring during whooping cough. Mojumdar²⁴ has found that 41 per cent of encephalopathic complications occurring in the course of pertussis were observed in patients under the age of 2 years, the period when most fatal cases occur. According to this author, next to pneumonia, convulsive phenomena are the most common fatal complications.

Lurie and Levy²⁵ have studied personality changes following pertussis in a group of 500 problem children investigated at the Children's Guidance Home in Cincinnati. Among this group there were fifty-eight children who had been ill with whooping cough at the age of 2 years or younger. In 8.6 per cent of the group (of fifty-eight children) the authors felt there was a definite relationship between the attack of whooping cough and the behavior disorders which were responsible for referral of these patients to the Guidance Home. It is felt that the results of Lurie and Levy are inconclusive. In any unselected group of 500 children one would expect to find a history of pertussis in at least fifty-eight. Also, the entire group was made up of children with behavior disorders, so that it is inescapable that a history of pertussis could accompany the occurrence of behavior disturbances in at least part of the group. It would be more appropri-

ate to start with a group of children who are known to have had severe pertussis in infancy and then to study them at intervals of five and ten years in order to evaluate their subsequent progress and to compare their development with the parallel development of their siblings.

A follow-up study dealing with the patients here reviewed is now in progress. It is planned to do physical examinations, psychological examinations, and laboratory studies on all the patients whom we are able to re-examine. We are especially interested in discovering the existence of any chronic respiratory disease in the patients known to have had severe pertussis. We plan also to evaluate their social and educational development in terms of the absence or presence of behavior disorders, and school progress. It will be especially worth while to compare them in these respects with children who may have escaped the disease at comparable age periods.

DISCUSSION

In the absence of any predetermined experimental plan, it is impossible to evaluate serum therapy in the present study. There has been no significant difference between the serum-treated and the non-serum-treated patients in terms of fatality rate since 1941, when serum was first introduced, but during that time serum has been given to the more severely ill patients, so that no adequate controls are available. In the whole period, 1931 to 1945, the fatality rate in the larger no-serum group was significantly higher than in the severely ill group of patients receiving serum after 1941, but factors such as the general decline in pertussis mortality and improvements in supportive therapy may explain this finding. Other criteria, such as gain or loss in weight, or duration of hospitalization, have failed to show significant differences in favor of serum therapy. We have not found it possible to keep sufficiently accurate records of the number of coughing paroxysms or cyanotic episodes occurring each day to use these direct manifestations as criteria of the progress of the disease. Perhaps a follow-up study may reveal differences, in either the incidence of chronic respiratory disease or in psychological development, which may serve as criteria for the severity of the acute disease. From the standpoint of the patient as a whole these may be the most important aspects of pertussis, and therapy should be evaluated in terms of its ability not only to lower mortality but also to diminish prolonged impairment of health or reduction of intellectual capacity.

The care and management of infants with pertussis have undergone considerable change during the past two decades. No doubt our increased understanding of infant physiology has been a most important factor in the improved management of all diseases occurring during infancy. The fact that no fatal case of pertussis has occurred at The Infants' and Children's Hospitals in the past four years is probably significant, we feel, for reasons other than whatever value may be placed on serum therapy.

In this report little has been said concerning the prophylactic value of pertussis hyperimmune serum because we have had no experience with it. In several studies cited, the prophylactic value of the serum has been pretty clearly established.

SUMMARY AND CONCLUSIONS

1. An analysis has been made of 137 cases of pertussis in infants under 2 years of age admitted to The Infants' and Children's Hospitals between 1931 and 1945, forty-five of whom were treated with pertussis hyperimmune serum during the period 1941 to 1945.

2. The types of therapeutic procedures employed in the treatment of pertussis during the past fifteen years are reviewed.

3. It was not possible to prove or disprove the value of serum treatment from a study of such a small group of cases, although the case fatality rate has declined since its introduction.

The writer wishes to express his indebtedness to Dr. Charles A. Janeway, Dr. Gretchen H. Moll, and Dr. Jane Worcester for their assistance in the preparation of this report.

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STOOL EOSINOPHILIA IN GASTROINTESTINAL ALLERGY OF INFANCY

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MANIFESTATIONS of gastrointestinal allergy are quite frequent in infancy. The symptoms—colic, intermittent diarrhea, and retention-type vomiting—are so well known that the diagnosis is usually eventually made by the alert pediatrician, particularly if all the symptoms occur together or there is a convenient facial eczema to point an accusing finger. However, all these symptoms may have other causes: "Colic" may be due to anything from hunger or inept handling by the mother to hypersecretion and hypermotility calling for the use of antispasmodics; the diarrhea frequently suggests infectious diarrhea or even celiac disease; the vomiting is often indistinguishable in type from that of pylorospasm or pyloric stenosis. The long period of trial and error involved in making a differential diagnosis often leads to despair on the part of the mother and a change of doctors.

The desirability of a quick and easy method of spotting gastrointestinal allergies is, therefore, obvious. Such a method is available in the examination of the stool for the presence of eosinophiles.

Many years ago Haughwout¹ called attention to the presence of large numbers of eosinophiles in the stools of patients suffering from diarrhea caused by gastrointestinal allergy. This phenomenon has proved of considerable usefulness in the differential diagnosis of diarrheas.² It recently occurred to me that it would be worth while to look for eosinophiles in the stools of infants showing other symptoms suggestive of gastrointestinal allergy. The results have been very gratifying, as the following case reports will show.

CASE REPORTS

Group I. Simulation of Pyloric Stenosis

CASE 1.—G. II., a female infant, was apparently normal at birth. She was fed on an evaporated milk mixture and gained 2 pounds in the first month. At 5 weeks of age she began to vomit with increasing frequency; vomiting was projectile in type and included large amounts of curdled milk, even when vomiting followed immediately after feeding. Stools were said to be normal. When she was seen at the age of 6 weeks her weight was the same as it had been at one month.

On examination there was visible gastric peristalsis, but no pyloric tumor was felt. Stools showed an excess of mucus, which, on staining, showed numerous eosinophiles.

Evaporated goat's milk was substituted for evaporated cow's milk in her formula. No other treatment was given. Vomiting promptly stopped, and eosinophiles were no longer found in the stool.

¹From the Department of Pediatrics, The Medical Group, Honolulu.

Group II. Diarrhea and Vomiting

CASE 2.—G. V., a male infant, was first seen Jan. 24, 1948, at the age of 4 months with the complaint of vomiting and frequent small stools of three weeks' duration. Vomiting was projectile in type. The infant had been breast fed until the age of 3 weeks, after which he had been weaned to evaporated milk formula, on which he apparently did well until the onset of the present illness. Substitution of rice water for his formula controlled the symptoms, which recurred whenever milk was again given.

Examination showed moderate dehydration and a considerable degree of malnutrition (birth weight was 8 pounds and the weight at 4 months was 10 pounds 2 ounces). Stools showed an excess of mucus, which, on staining, was loaded with eosinophiles with a few pus cells.

He was put on a soybean formula (Mull-Soy) and a vitamin concentrate. Diarrhea and vomiting promptly stopped. When he was seen again in three weeks, his weight was 12 pounds, 5 ounces, and solid foods were added to his diet without recurrence of symptoms.

CASE 3.—B. L., a female infant, was seen at the age of 3 weeks with the complaint of vomiting and the presence of blood and mucus in the stools, following a shift from breast feeding to a cow's milk formula. Examination was normal except for the stools, which showed a large amount of bloody mucus which, on staining, was loaded with eosinophiles.

She was put on a soybean formula without improvement. The mother, on her own, then tried Olac and S-M-A without any change. Stools still showed many eosinophiles. She was then put on an evaporated goat's milk formula, after which all symptoms cleared. At the age of 10 months she was able to go over to a cow's milk formula without recurrence of symptoms.

Group III. Colic

CASE 4.—S. L., a female infant, was seen May 27, 1947, at the age of 12 days, with the complaint of violent crying after every feeding. Vomiting and diarrhea were not present. Examination was negative except for the stools, which showed numerous eosinophiles in the stained mucus. Formula was changed to Nutramigen with immediate relief of symptoms.

CASE 5.—R. K., a 2½ pound premature male infant, was under my care from birth. He had an uneventful hospital course, gaining well on an Olac formula and was discharged at the age of 2 months weighing 5½ pounds. As usual the undue amount of crying was not noted in the hospital. After one week at home the family was in a state of exhaustion, for the infant, while gaining well and not vomiting, "screamed from morning to night."

Examination was normal except for the stools, which contained an excess of mucus which was loaded with eosinophiles when stained. The formula was changed to Nutramigen, and all symptoms subsided.

Group IV. "Colic" and Diarrhea

CASE 6.—S. L., a female infant, was first seen Sept. 25, 1947, at the age of one month, with the complaint of excessive crying after feedings and frequent small mucoid stools. She had been bottle fed on an evaporated milk formula from birth. Examination was negative except for nasal obstruction and the presence of eosinophiles in the stools. The formula was changed to Nutramigen and subsequently to Mull-Soy without relief of symptoms. Eosinophiles persisted in the stool. On Oct. 24, 1947, she was put on evaporated goat's milk, and all symptoms were relieved.

CASE 7.—S. D., a female infant, was seen at the age of 2 months with the complaint that "she cried all day long," and had had a diarrhea for the preceding four days. She had been fed on almost every known brand of dried and liquid cow's milk without any improvement and had been given large doses of phenobarbital without relief.

Examination was negative except for the stools, which showed large amounts of mucus containing many pus cells and eosinophiles. It was felt she had both infectious diarrhea and gastrointestinal allergy. All symptoms cleared in forty-eight hours on a change to a goat's milk formula plus small doses of sulfadiazine, the necessity for which is debatable. This infant is still, at the age of 16 months, unable to take any form of cow's milk without a recurrence of diarrhea.

CASE 8.—C. T., a female infant, was first seen Feb. 4, 1948, at the age of 11½ months. She had been fed on an evaporated milk formula from birth and was doing well. Orange juice and cod liver oil were prescribed at that time.

Seen again on February 19, she was "crying all the time" and having frequent mucoid stools. Examination showed an early facial eczema and many eosinophiles in the stools.

A vitamin concentrate was substituted for the orange juice and cod liver oil. This resulted in prompt clearing of symptoms and disappearance of eosinophiles from the stools.

Group V. Simulation of "Celiac Disease" and Fat Intolerance

CASE 9.—K. M. was first seen Sept. 25, 1947, at the age of 4 months, with the complaint of frequent, large, pale bowel movements and failure to gain weight. The symptoms had been present with gradually increasing severity since the age of one month. The infant had been bottle fed since birth. Stools were said to be normal when skimmed milk was fed, but there had been no weight gain for one month. There was no colic or vomiting.

Examination showed an undernourished infant with a protuberant, gassy belly. Stool (even on skimmed milk) was pale, foamy, and loaded with fatty acids and neutral fats. The findings were so apparently typical of celiac disease that no stain for eosinophiles in the stools was made, and treatment was confidently started with crude liver extract and fat-free diet.

The usual dramatic response failed to appear: After three weeks the stools had not changed and only 8 ounces of weight had been gained. At this time the

stool was first examined for eosinophiles, and they were found in large numbers in the mucus. The formula was changed to goat's milk without improvement or weight gain after one week. Numerous eosinophiles were still present in the stool. A change to Mull-Soy brought immediate improvement; eosinophiles and excess fats and fatty acids disappeared from the stools in two days, and a weight gain of 2 pounds occurred in two weeks. The subsequent progress (age now 10 months) has been normal.

CASE 10.—P. A., a female infant, bottle fed from birth, was first seen Jan. 21, 1948, at the age of 5 weeks. The complaint was of poor weight gain. The weight was 8 pounds, as compared with a birth weight of $7\frac{1}{2}$ pounds. Stools were said to be normal. The formula was an extremely dilute evaporated milk mixture, and it was felt that the failure to gain was explained by an insufficient calorie intake. An adequate evaporated milk formula was prescribed. Seen one week later the infant was gaining poorly, and stools were pale and mushy, showing an excess of fatty acids. On a diagnosis of "fat intolerance," the formula was changed to Dryco. A good weight gain followed: On March 1 the weight was 11 pounds, 13 ounces, and stools were said to be "frequent, but of good color."

By March 10 this frequency had increased to eight to ten daily, and the weight gain had stopped. Stools were for the first time examined for eosinophiles, and they were found in large numbers. The formula was changed to evaporated goat's milk, and within two days the stools were normal in number and free of eosinophiles and excess fats.

CASE 11.—M. F., a male infant, was seen in consultation at Children's Hospital at the age of three months, with a history of large, frequent, loose stools and failure to gain weight. He had been a "feeding problem" from birth, with a tendency to diarrhea on the many formulas (all derived from cow's milk) which had been tried.

Stool examination in the hospital had shown great excess of fats and fatty acids, and a diagnosis of celiac disease had been made. No response was obtained from parenteral liver extract, large doses of B-complex, and a fat-free formula.

On examination he was only one pound over birth weight ($8\frac{1}{2}$ pounds), was markedly undernourished, and had a protuberant, gassy abdomen. The stool showed massive numbers of eosinophiles in the stained mucus.

A diagnosis of gastrointestinal allergy was made, and the use of a Mull-Soy formula was suggested. Within three days the diarrhea was controlled, and within two weeks he had gained 2 pounds.

DISCUSSION

These illustrative cases have been selected from over thirty patients in my practice in the past two years who have shown eosinophilia in the stools. They represent a group of patients who are frequently found in any pediatric practice. I believe the diagnosis in all the cases would have been made eventually without examining the stools for eosinophiles, but in the majority a long period

of trial and error was eliminated. In the three patients in Group V, a great deal of grief for doctor and patient could have been avoided by looking for stool eosinophiles on the infant's first visit.

TECHNICAL DATA

Beautiful preparations to demonstrate eosinophiles in stools can be made by wet fixation of films of mucus in Schaudinn's solution and staining with Giemsa. However, this method is time-consuming and requires equipment not available in every doctor's office. A satisfactory, rapid method is as follows:

1. Stool specimen is generally obtained by inserting a gloved finger into the infant's rectum; the "suppository" action will usually produce enough material for examination.

2. Mucus is carefully picked free of stool material with fine forceps and placed on a glass slide.

3. A cover slip is dropped on the mucus and the preparation examined under the microscope to determine whether cells are present.

4. If cellular material is present, a film is made by gliding the cover slip off the slide.

5. The slide is then immediately heat-fixed over a flame.

6. Wright's stain is flooded onto the slide while it is *still hot*, and immediately diluted with water or buffer solution.

7. Allow to stain until the surface of the liquid is covered with a greenish opacity.

8. Wash, dry over a flame, and examine under cedar oil. The entire process takes less than five minutes.

CONCLUSION

Examination of the mucoid portion of stools for the presence of eosinophiles is of value in recognizing gastrointestinal allergy in infants.

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THE TREATMENT OF EPIDEMIC VOMITING IN PEDIATRIC PRACTICE

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VOMITING is a common initial symptom in the acute infectious diseases of children. This is particularly true in diseases of the respiratory tract. However, cases are often encountered in which it is difficult to find any evidence of infection that is responsible for the vomiting.

In Baltimore and its environs it has been the experience of pediatricians and general practitioners of medicine to see individuals who repeatedly vomit for twenty-four hours or longer without exhibiting any positive physical findings. The syndrome, while most prevalent in children, also occurs in adults, but seldom occurs in infants under 6 months of age. It has a rather striking seasonal incidence, being seen almost entirely during the months of October and November, and then disappearing with the onset of seasonably cold weather. However, when the weather is unseasonably warm, it will continue through December and January or until the appearance of cold weather.

The onset is quite abrupt. A previously well child will suddenly begin to vomit, usually with no preceding complaint of nausea. The patient then continues to vomit at frequent intervals. An associated retching is seen in those individuals who are emotionally of high timbre. All of the patients have an insatiable thirst and constantly crave water, which, when given, is promptly vomited. The vomiting, as a rule, subsides within twenty-four hours, with, in the main, no aftermath other than a slight indisposition and anorexia lasting for several days. During the fall and winter of 1946-1947, respiratory infections seemed to follow the onset of vomiting in about seven days. These were manifested by a rather severe tracheobronchitis of stubborn duration and very often a complicating otitis media. This was so constantly observed that the connection between vomiting and respiratory infection seemed an inevitable conclusion. However, in other years, no connection could be established with any subsequently appearing respiratory infection.

The infectiousness of the disease is well illustrated by the rapid appearance of vomiting within twenty-four to forty-eight hours in other members of the family.

Abdominal pain is often encountered and is localized by the patient in the left quadrant. It is fleeting in type and not too severe. The umbilicus is also given by many children as the site of the pain.

Diarrhea is usually not associated with the vomiting. The stools, seldom numbering more than three per day, are light in color, almost white, and have an extremely foul odor. The odor disappears in several days with appropriate dietary measures, but the color persists for four or five days.

The temperature is seldom elevated beyond one or two degrees and in the majority of cases is usually normal. Those who have an elevation of temperature maintain it for only twenty-four or forty-eight hours.

Physical examination is completely and entirely negative. Transient glycosuria causing a trace to three-plus reduction is seen in the majority of patients.

The blood findings are not remarkable. There is usually a slight reduction in the total number of leucocytes, with a relative increase in the granulocytes. Reimann and his associates,⁴ however, reported leucocytosis in their series.

While most of the cases are of short duration, there are occasionally some that seem to be prolonged. The following are three cases that seemed to have had their origin with the vomiting previously described:

CASE REPORTS

CASE 1.—B. G., aged 3 years, was seen on Jan. 3, 1942, because of occurrence of glycosuria, found on repeated examinations by her family physician. In November of 1941, the child had a period of vomiting for forty eight hours. Following the cessation of vomiting, she complained of vague abdominal pain, developed marked anorexia, frequently complained of nausea, and on several occasions vomited. It was also noticed that the stools were very pale in color and of particularly foul odor. A low grade fever seemed to persist for several weeks. Physical examination through this period and at the time of admission was essentially negative. It was felt advisable that this child be admitted to the hospital for study. The results were as follows:

Urinalysis showed a three plus sugar on only two occasions, and both of these were on nonfasting specimens. All fasting specimens were negative for sugar. Nonprotein nitrogen determinations were 25 and 34 mg. per cent on two occasions. The blood amylase gave a reading of 142. The results of the glucose tolerance test were as follows:

Fasting blood sugar	74 mg.
½ hour	164 mg.
1 hour	278 mg.
2 hours	264 mg.
3 hours	180 mg.
4 hours	155 mg.

The urine specimens collected gave a two plus reduction test at the first, second, and third hours. The blood count was essentially normal, with a hemoglobin value of 14 Gm., and with leucocyte and differential counts giving entirely normal values.

The patient, who had been on a restricted carbohydrate diet, was placed on a high thiamin chloride, low fat, low residue, high carbohydrate diet, with tincture of belladonna, mints 5, t.i.d., a.e., and discharged. The child's appetite improved, the stools returned to normal, and she seemed quite well within three weeks. At the end of six weeks, after repeated urinalyses had failed to show the presence of sugar, other than one plus following meals, the glucose tolerance test was repeated and the curve found to be within normal limits. This patient has continued quite well.

CASE 2.—M. H., 5 years old, was referred because of anorexia and the frequent occurrence of glycosuria of three months' duration. She was first seen in March of 1942. Further history added only the presence of low grade fever for three weeks following the onset of an episode of vomiting of forty eight hours, and it was noted that the mother, father, and an older sister also had vomiting at this time. This was attributed by the parents to some dietary indiscretion. Following the vomiting, it was then noted that the anorexia and glycosuria occurred. The patient was admitted to the University Hospital for observation. The results of the hospital study were as follows: Repeated examination of fasting urine specimens gave a one plus reduction for sugar. The glucose tolerance test was as follows:

Fasting blood sugar	80 mg.
½ hour	155 mg.
1 hour	200 mg.
2 hours	196 mg.
3 hours	170 mg.
4 hours	130 mg.

The collected urine specimens showed the fasting urine to have no sugar, but the one- and two-hour specimens gave a two-plus reduction; the others were negative. The blood amylase was 154 in this patient. Other findings were noncontributory. The patient was discharged on a high thiamin chloride, low fat, high carbohydrate, low residue diet, with pancreatic extract, grains 5, t.i.d., a.e. The patient was seen again in six weeks, her appetite had improved, and for the last four weeks there had not been any glycosuria. A repeated glucose tolerance was done at this time, and the curve found to be perfectly normal.

CASE 3.—R. B., 16 months old, began to vomit following the other members of the family. Despite all medication, the vomiting persisted, and the infant was seen by me on Dec. 18, 1942. Physical examination demonstrated only a markedly dehydrated infant with a temperature of 103° F. The patient was hospitalized at the University Hospital. The admission blood sugar was reported at 284 mg. Before the blood sugar was reported, 250 c.c. of 10 per cent glucose had been given intravenously. The following morning the blood sugar level was 78 mg. The subsequent course was uneventful, and the patient was discharged on Dec. 24, 1942.

These cited cases seem to have had their onset as a result of infectious vomiting. The temporary derangement of carbohydrate metabolism is interesting and it would have been quite simple to have diagnosed the first two cases as low-threshold diabetes, had it not been subsequently determined by course and blood sugar check to be otherwise. Unfortunately, biochemical studies have not been made on the majority of patients with epidemic vomiting, for they, as a rule, promptly recover.

Many of the cases of epidemic vomiting are considered by parents to be purely the result of faulty food intake, a conclusion they derive from the fact that all members of the family are affected with the same malady. This makes it difficult to give any accurate estimate as to the frequency of actual occurrence. However, I have accumulated, from private practice, a total of 773 cases as shown in Table I. This figure shows that the disease is very frequent, and also as gathered from the table, that it makes a fairly constant yearly appearance.

TABLE I. OCCURRENCE OF EPIDEMIC VOMITING IN 773 PATIENTS

YEAR	NUMBER OF CASES
1940-41	103
1941-42	96
1942-43	109
1943-44	167
1944-45	126
1946-47	182
Total	773

The case of epidemic vomiting as seen in the child, if treated properly responds promptly and need not occasion any alarm. Restriction of fluid by

mouth in large quantities is necessary because, if given, it is promptly vomited. While Brennemann⁵ states that fluid by mouth which is eventually vomited is useful in washing out the stomach, it also creates an unnecessary chloride loss. A high carbohydrate intake is desirable. The frequently advocated orange juice fortified with sugar is not tolerated. Lollypops or all-day suckers are occasionally found to be of some help. Sedation obtained by the use of paregoric or phenobarbital is generally not of any value.

The treatment that I have found without exception to be satisfactory is as follows:

Coca-Cola syrup (obtained at the drugstore fountain) is given in teaspoonful doses at intervals of fifteen to thirty minutes until three or four doses have been retained. Nothing other than the Coca-Cola syrup is permitted. This must be stressed to the parent. Usually, there is no further vomiting after the first dose of Coca-Cola syrup. Then, one teaspoonful is given every three hours for the next forty-eight hours. Following the initial treatment with Coca-Cola syrup, the patient is then permitted such foods as apple sauce, gelatin products, precooked cereals with only added sugar, toast or crackers, and jelly. The only fluids permitted for the remainder of the twenty-four hour period are tea, cracked ice, and very small, frequent sips of water. After the initial twenty-four hour period of treatment has been completed, additions to the diet then consist of skimmed milk, fruit juices, with the exception of orange juice, cooked cereal, strained broth, and baked potato. The continuation of a low residue, low fat, high carbohydrate diet is advisable for at least four days after the onset of the vomiting.

The preceding treatment will be found to be very satisfactory and, if used as outlined, will give uniformly prompt results. I have tried all of the suggested treatments as given by various authorities for the treatment of vomiting and have found no other to be as practically useful as this one. I can only speculate as to why the Coca-Cola syrup is effective in the control of vomiting. It must be the xanthine content that is primarily responsible by its effect on the smooth muscle of the stomach. Therapeutic doses of the xanthines have no significant effect on gastric activity. However, high concentrations do depress the tone and amplitude of contractions of isolated intestinal strips, so it would seem not unlikely that the Coca-Cola syrup reduces the gastric tone. This may explain its effectiveness in the control of vomiting.

The syndrome is called by a variety of terms, the most common being "intestinal flu." The literature is replete with descriptions of seasonal emesis under such terms as seasonal gastroenteritis,¹ Spence's disease,² and acute infectious gastroenteritis.³ Reimann and his co-workers⁴ reported extensively upon "epidemic diarrhea, nausea and vomiting of unknown cause," which occurred in the Philadelphia area in the fall of 1943 and again in 1944. Their attempts to determine an etiological agent were fruitless. Finkelstein is quoted by Brennemann⁵ as speaking of Beech epidemic or epidemic of vomiting. Brennemann⁵ himself speaks of vomiting only in association with evident infectious diseases. Whether it is a distinct entity or not will be determined only through biochemical and bacteriologic studies. However, at the present it seems appro-

priate to recognize a disease that is characterized by vomiting and low-grade fever, with occasional temporary carbohydrate disturbance, and one that is infectious. Therefore, until many findings are clarified, the term "epidemic vomiting" seems appropriate for this syndrome.

SUMMARY

1. A report of 773 cases of an infectious type of vomiting is given.
2. A definite clinical entity is assumed.
3. It is of very frequent occurrence in private practice of pediatrics.
4. The successful control of the vomiting with the use of Coca-Cola syrup is described.

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TORSION OF THE SPERMATIC CORD IN THE NEWBORN INFANT

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TORSION of the spermatic cord, or, as commonly designated, torsion of the testicle, is an axial rotation of the testicle and epididymis or, as in the cases here reported, of the entire scrotal contents with a cutting-off of the blood supply. Unrelieved, this results in hemorrhagic infarction of the strangulated structures and, if infection exists, suppurative gangrene. The disease is predominantly one of the later years of childhood and the earlier years of adulthood; O'Connor¹ found the average age incidence to be 13 years and 4 months. Yet the occasional observation of unilateral atrophic testis in boys with a classical history of torsion years previously suggests that the condition occurs sufficiently often to demand its diagnostic consideration when acute scrotal swelling occurs in the newborn or young infant.

The earliest record of this condition in the newborn infant is that of Taylor,² in whose patient the acute condition was noted when the boy was 4 hours old. Trillot³ encountered it in a 3-day-old male, and others have recognized it in subsequent months. Allen and Andrews⁴ had three cases at Bellevue Hospital in infants under 12 months of age. Donovan⁵ collected 163 cases, of which thirteen were in children under one year of age. My two cases are apparently the second and third to be reported in which the torsion occurred during the first day of life. They were necessarily treated by castration on the third and seventeenth days of age respectively. Moreover, these two cases are of special pathologic interest because the torsion occurred outside the tunica vaginalis (Figs. 1 and 2)—a condition denied by many to occur.

ETIOLOGY AND PATHOLOGY

Torsion of the spermatic cord occurs more often on the right side, and in about 5 per cent of the reported cases has been bilateral. The torsion can occur in either direction and even through two or more complete turns. The direct cause of torsion of the spermatic cord is unknown, and the usual hypothesized factors concerned with its occurrence in older patients probably do not hold during the neonatal period. In older patients, the genesis of the condition has been attributed to a variety of conditions which afford unusual testicular mobility, and are chiefly maldescent, lack of a gubernaculum, lack of attachment to the tunica vaginalis, anomalous formation, or undue spaciousness of the tunica vaginalis. Sudden strain and/or spontaneous contraction of the cremasteric muscle is believed to bring about the twist, in some unknown way. Yet in many instances the torsion has occurred during sleep. In about 500 reported cases (thirty in my experience) there has been an anomalous development, predominantly of the testicle-epididymis relationship, and characterized in the main

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by an unusually long mesorchium. In many of these, the testicle previously had been observed to be abnormally mobile or imperfectly descended. Yet in the newborn infant with extratunical torsion and with the possible exception of testicular maldescent, these anatomic explanations defy practical clinical consideration.

When the condition occurs in older patients, the site of the torsion is regularly within the tunica vaginalis, but in Taylor's case² and in both of mine, the twist occurred outside of the tunica vaginalis (Figs. 1 and 2). This observation affords special etiological interest and clinical distinction. Long ago Sir Ashley Cooper noted that the entire scrotal contents of the newborn infant could be freely lifted out of the scrotum without tearing of tissue, and this explains how torsion including the tunica vaginalis can occur. Presumably cremasteric contraction is the impelling force producing the twist. In mild torsion with incomplete shutting-off of the blood supply, the late result is mild atrophy of the testicle. In complete and unrelieved strangulation, the testicle and epididymis proceed to hemorrhagic gangrene, subsequent atrophy, and isolated sterility. Occasionally the testicle disappears entirely. Microscopically, the testes and epididymis show extensive hemorrhagic necrosis with widespread red blood cell infiltration. The late picture is that of advanced universal fibrosis with corresponding loss of spermatid and tubular elements. Even with prompt detorsion, some atrophy usually follows.

SYMPTOMS

The usual onset of torsion of the spermatic cord is sudden with excruciating pain in the testicle, which may be referred to the inguinal region, over the iliac crest, or to the abdomen. Gastrointestinal disturbances, notably nausea and vomiting, generally occur and, when the testis is improperly descended, may suggest incarcerated inguinal hernia. When the testis is in the scrotum there is pronounced painful swelling of the involved side, but this is localized to the scrotum. The condition may simulate orchitis, epididymitis, torsion of the testicular appendage, strangulated hernia, or, in the newborn infant, hemorrhagic infarction of the testicle. With complete infarction due to torsion, the testicle ultimately may become nearly insensitive. The systemic manifestations are those common to toxemia, although fever is low or absent.

DIAGNOSIS

The sudden onset of acute scrotal swelling in a young person without nongenital infection at once suggests the diagnosis of torsion of the spermatic cord. The prostate will feel normal. Acute hydrocele may preclude differentiation between epididymis and testicle, and sanguineous fluid in the tunica vaginalis will prevent transillumination. When the upper end of the epididymis is involved in the twist, palpable swelling of the tender peripheral segment of this organ will suggest epididymitis. In torsion, the scrotal skin is less likely to be adherent to the underlying structures than it is in acute epididymitis. Prelim⁶ observed that elevation of the involved testicle relieves the acute pain of epididymitis but not of torsion. In newborn infants the acuity of the pain is such

that they obviously do not wish to move, to be moved, or to have their genitalia handled. If the testicle is undescended in the inguinal canal, the acute manifestations are localized to the groin, and in the rare instances of torsion of an intra-abdominal testicle, the diagnosis of acute surgical intestinal disease is generally made. Recently in a 5-month-old boy with right undescended testicle and acute swelling near the internal inguinal ring, the clinical manifestations made the diagnosis of torsion of an undescended testicle seem unquestionable. Yet exploration disclosed strangulated hernia with inclusion of the undescended testicle in the acute fibrinous reaction. Reduction of the hernia, fortunate restoration of circulation of the strangulated 6-cm.-long loop of gut, and fixation of the testicle in the lower scrotum were curative.

In torsion of the spermatic cord the white blood count is generally under 15,000 and rarely over 20,000 cells per cubic millimeter, but the polymorphonuclear count will be elevated to 60 to 90 per cent.

TREATMENT

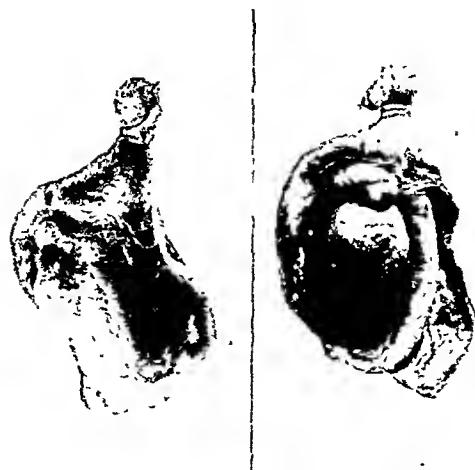
If the patient can be operated upon within four hours after the acute onset surgical detorsion will usually conserve the organ. Yet partial testicular atrophy may be expected to reflect the damage caused by the temporary strangulation of the spermatic cord. In a few instances spontaneous detorsion has occurred, and in others prompt manual untwisting has relieved. Unfortunately most patients with torsion are treated for days with ice caps, coal-tar analgesics, and vain hope, so that with the usual delay castration is demanded. When the opposite testicle is abnormally mobile, it should be fixed to the lowermost scrotum to prevent subsequent torsion on this side, as I have observed to occur in two young men, one of whom thereby became a eunuch. In Case 1, to be described, the surgical treatment was carried out, under local anesthesia, when the child was 3 days old.

CASE REPORTS

CASE 1.—R. G. was delivered by normal birth on June 2, 1946. Twenty-four hours post partum his nurse noticed the right scrotum was swollen and apparently tender. On the third day I saw the child in consultation and found the right scrotum swollen to approximately four times normal size. The overlying skin was edematous and firmly attached to the underlying structures, and acute hydrocele precluded deep palpation. At the upper pole of the scrotum the cord was tender and thickened, but not at its entrance to the external inguinal ring. Temperature was normal.

The blood count was as follows: hemoglobin 19.5 mg. (130 per cent); red blood cells 5.46 million; white blood cells 15,850; polymorphonuclears 89 per cent; lymphocytes 9 per cent; myelocytes 2 per cent. There was a severe shift (Schiller) to the left and mild toxic granules.

A diagnosis of torsion of the spermatic cord was made. Without delay and under local anesthesia, using 0.5 per cent novocain hydrochloride solution, the scrotum was opened. The tunica vaginalis was found tensely distended and blue. On opening it, about 2 c.c. of bloody hydrocele fluid gushed forth, and the testicle and epididymis were each found enlarged about three times and mahogany color. Further examination disclosed a clockwise torsion of the spermatic cord of 180 degrees just outside the tunica vaginalis (Fig. 1); the spermatic cord above this point was normal. Orchidectomy was performed. Convalescence was uneventful, and the child was discharged home with his mother one week later.



A.

B.

FIG. 1.—A. Torsion of the spermatic cord in Case 1 showing twist outside (above) the tunica vaginalis. B. Hemorrhagic infarction of involved structures. Note 180 degree twist of cord at upper pole as well as the great swelling of the epididymis and thickening of the tunica vaginalis.



A.

B.

FIG. 2.—A. Torsion of spermatic cord in Case 2 with twist outside tunica vaginalis. B. Because of infection and greater duration of the condition, the indurated tunica vaginalis is six times normal thickness. The epididymis is gangrenous, as is the shrunken testicle.

CASE 2.—J. L. On May 3, 1947, I was called in consultation to see this 17-day-old boy who presented a hard, right scrotal swelling about 3 by 2.5 cm. and with an obvious abscess measuring 1.5 by 1.5 cm. at the lower scrotal pole. There was marked serotal redness together with mild inguinal lymphadenitis. The testicle and epididymis could not be differentiated, and the lower half of the scrotum was adherent to the underlying structures. At its entrance to the external inguinal ring the spermatic cord was normal. Rectal examination was negative. The history was elicited that the day after birth a swelling of the right scrotum was noted, but received no attention other than wet dressings until the sixth day when the family physician, an osteopath, thought the boy might have a tumor of the testicle. An aspiration biopsy was performed, which apparently succeeded only in introducing infection and which ultimately

resulted in the previously described lower polar serotal abscess. Eventually a pediatrician, Dr. William Matthews, was called in consultation, and he in turn called me; a tentative diagnosis of torsion of the spermatic cord was made.

The child was taken at once to the hospital (the age then 17 days). The red blood cell count was 4.13 million; hemoglobin 11.6 Gm. (77.3 per cent); leucocytes 20,000, with 61 per cent polymorphonuclears and 39 per cent lymphocytes. Under open drop ether anesthesia the right scrotum was opened with a racquet-shaped incision which excised the necrotic lower serotal pole and liberated about 2 c.c. of pus. The local pathologic change was a duplication of that described in Case 1 except that hemorrhagic gangrene of the testicle and epididymis was more advanced and the tunica vaginalis was greatly thickened. Likewise, the twist was extravaginal just above the point of attachment of the tunica vaginalis to the spermatic cord, and of a slightly greater degree than in Case 1 (Fig. 2). Orchidectomy was performed, and the scrotum was closed about a small Penrose drain. Convalescence was uneventful, afebrile, and the infant was discharged home three days later.

SUMMARY

Attention has been directed to the occurrence of torsion of the spermatic cord during the first day of life in two cases and terminating in loss of the testicle. In each instance, the twist occurred outside the tunica vaginalis. If the condition is recognized and detorsion can be performed during the first four hours, the testicle usually can be preserved. Diagnostic and therapeutic delay means loss of the organ.

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CALCIFIED INTRACRANIAL TUBERCULOMAS

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INTRODUCTION

THOUGH tuberculomas of the brain have been observed less frequently in recent decades, their clinical recognition and occurrence in autopsy material is not uncommon. Wilson and Bruce,¹ in a collective review of recent statistics, concluded that intracranial tuberculomas constitute 3.6 per cent of verified brain tumors. Nearly half of the tuberculomas of the brain have been encountered in patients under 10 years of age,² indicating that this condition is of relatively greater importance during childhood. Calcification in these lesions has been described as an apparently infrequent phenomenon. Scott and Graves,² in a review of 815 cases of intracranial tuberculomas, noted calcification in only eleven cases. In a recent survey by Weinberger and Grant³ in 1942, nineteen verified cases of calcified intracranial tuberculomas were collected from the literature, to which the authors added one case of their own. Since publication of this paper, I have been able to find three additional cases in the literature.^{4, 5}

This rare occurrence of calcified tuberculomas of the brain is surprising, considering the fact that calcification is not an uncommon event in tuberculous lesions of other organs. It has been suggested that some of these lesions may remain unrecognized during life in the absence of roentgenographic studies.⁶

Cerebral tuberculomas have received renewed interest, since it has been shown that surgical procedures in this condition are not necessarily followed by fatal meningitis but may prove to be of therapeutic value in selected cases.⁷ This should apply particularly to calcified or ossified lesions in which a tendency towards healing and encapsulation is conspicuous. It remains in the realm of speculation whether with advances of antibiotic therapy, healing and calcification in cerebral tuberculomas will occur more frequently, making it feasible to recognize them on roentgenologic examinations. From the diagnostic standpoint, calcified tuberculomas of the brain are of importance since they present roentgenologic features which, in many instances, permit their differentiation from other calcifying intracranial lesions.³

For these reasons, it was considered of interest to record the following cases of calcified intracranial tuberculomas observed in childhood.

CASE REPORTS

CASE 1.—J. H., a 20-month-old Negro orphan girl, was admitted in September, 1943, because of pain and swelling of the left leg. Roentgenograms of the distal tibia revealed an oval-shaped cystic area of rarefaction, which was surrounded by slight bone sclerosis and extended into the epiphyseal plate. This process was interpreted as chronic osteomyelitis. Histologic examination of biopsy material from this lesion disclosed the presence of tuberculous granulation tissue and acid-fast organisms. Roentgenograms of the chest revealed calcium deposits in the right lower lung field and calcified mediastinal lymph nodes, but no definite active lesions in the lung parenchyma (Fig. 1). On a search for further bone lesions, roentgenograms of the skull were obtained, and a moderate number of small, serrated and

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angular, calcareous deposits were discovered in the cranial cavity (Fig. 2). These lesions were believed to represent intracranial tuberculomas.

There was considerable clinical improvement during the hospital stay. The patient was discharged in November, 1943, and subsequently seen on several occasions in the outpatient department.

In January, 1945, the child became suddenly ill with abdominal pain, nausea, and vomiting. On physical examination after hospital admission, she was found to stay on her side in a semicomatose condition with her legs and thighs flexed. The neck was stiff, and Kernig's and Brudzinski's signs were present. There were no remarkable chest findings, but the cervical lymph nodes were found to be enlarged bilaterally.

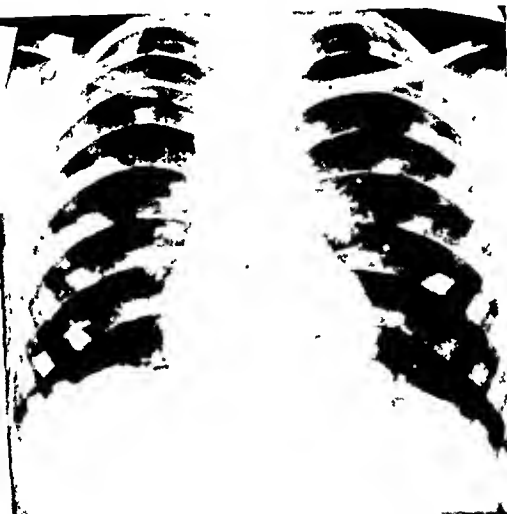


Fig. 1.

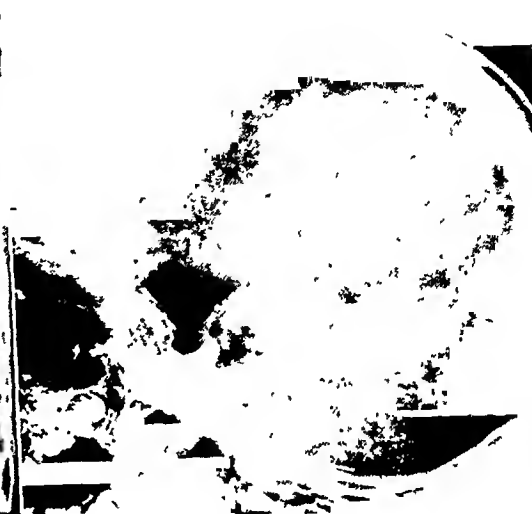


Fig. 2.

Fig. 1.—Case 1. Extensive calcification of mediastinal lymph nodes and calcium deposits in right lower lung field.

Fig. 2.—Case 1. Multiple intracranial tuberculomas. Note irregular and serrated contour of the lesions

The laboratory findings showed a normal red blood cell count and slight leucocytosis. The urine examination showed a few pus cells per high power field. The spinal fluid appeared clear and contained 1,168 white blood cells per cubic millimeter, with 98 per cent lymphocytes and 2 per cent polymorphonuclears. Smears of the spinal fluid did not disclose acid-fast organisms. The spinal fluid sugar was found to be 49 mg. per cent. A first strength tuberculin test was positive.

After a rapid downhill course the patient died on the fifth hospital day.

Essential Autopsy Findings.—Pleural adhesions were noted over both pulmonary apices. The tracheobronchial lymph nodes appeared enlarged, and one lymph node in the left hilum revealed extensive caseation. Calcium deposits were noted in both lungs and hilar lymph nodes. The heart, liver, pancreas, and kidneys were grossly not remarkable. The spleen contained several small yellowish nodules. The mesenteric lymph nodes were considerably swollen, but there was no caseation found on cut section. The brain weighed 140 Gm. The cerebrospinal fluid appeared cloudy and was increased in amount. The base of the brain was covered by a large amount of thick, gelatinous, greenish exudate, which extended laterally towards the sylvian fissures. Cut sections of the brain after fixation disclosed eleven calcified lesions in the gray and white matter of the cerebrum, the floor of the posterior horn of the right lateral ventricle, the pons, and the cerebellum. Histologic examination of the brain confirmed the gross anatomic diagnosis of tuberculous meningitis. The calcified masses were found to represent tuberculomas, varying in appearance from fibrosis to obvious activity.

Comment.—A 20-month old child with pulmonary and osseous tuberculosis was found to have on roentgenographic examination multiple calcified intracranial tuberculomas. The child remained free of cerebral symptoms for a period of observation of fifteen months, then developed fatal tuberculous meningitis. On autopsy, eleven calcified tuberculomas of the brain in various stages of activity were found.

CASE 2.—C. S., a 15-month-old Negro boy, was admitted on Aug. 2, 1945, because of recent lye burns of the lips, mouth and throat. On physical examination, numerous coarse and fine moist râles were heard over both lungs, and dullness was noted over the upper two-thirds of the right lung. The cervical and axillary lymph nodes were found to be enlarged. There were no unusual urinary findings, and the red blood count was within normal range. The white blood count disclosed 25,000 leucocytes with 1 per cent eosinophiles, 42 per cent polymorphonuclears, 56 per cent lymphocytes, and 1 per cent monocytes. The first- and second-strength tuberculin tests were negative. Roentgenographic examination of the chest two days after admission disclosed an extensive, rather homogeneous consolidation in the region of the right upper and right middle lobes. Aspiration pneumonia was considered likely, and the patient was treated with penicillin and sulfadiazine. This was followed by improvement in the general condition of the patient and satisfactory healing of the burns.



Fig. 3.

Fig. 3.—Case 2 Tuberculous osteomyelitis of right fifth rib. Tuberculous infiltration of right lung and extensive lymphadenopathy.



Fig. 4.

Fig. 4.—Case 2. Four calcified tuberculomas in posterior portion of cranial cavity.

After discharge from the hospital, the patient was seen on several occasions in the outpatient department. He was readmitted on March 1, 1946, because of extensive swelling of the neck. The temperature on this second hospital admission was 103° F., the pulse rate was 120, and the respirations were 28. The cervical lymph nodes were markedly swollen, and a hard, nonductuant mass was palpable in the region of the right mandible. Inspection of the mouth revealed several draining sinuses on the buccal surface of the right cheek and base of the tongue. A firm swelling about 3 cm. in diameter was noted in the posterior chest wall in the region of the fifth rib.

The laboratory studies on this admission revealed a strongly positive first-strength tuberculin test. The blood count was not remarkable.

Roentgenograms of the chest revealed an extensive consolidation throughout the right hilar area and right lower and intermediate lung fields, where there were several small calcified

deposits. The inferior aspect of the posterior portion of the right fifth rib showed an oblong area of destruction, surrounded by a large soft tissue mass (Fig. 3). There was no significant bone proliferation in this region. Roentgenograms of the mandible disclosed almost complete destruction of the right angle, with formation of numerous small sequestra. The roentgenologic examination of the skull disclosed four serrated calcium deposits, measuring approximately 5 mm. in diameter in the right parieto-occipital area of the brain (Fig. 4).

The presence of tubercle bacilli in the gastric contents was proved by guinea pig inoculation.

During a hospital observation of nine months, no remarkable changes in the patient's condition were noted. His temperature usually fluctuated between 99° and 103° F. Following discharge from the hospital the patient's family moved to another city. It was learned that he died in June, 1947. The exact circumstances of his death could not be ascertained.

Comment.—A 2-year-old child with pulmonary and osseous tuberculosis was found to have four calcified intracranial tuberculomas. There was no history of any symptoms referable to the central nervous system, nor did the patient develop any signs of intracranial disease during an observation of nine months. Though the calcified lesions of the brain cannot be considered proved tuberculomas, this diagnosis is highly probable in the presence of typical roentgen findings and active tuberculosis of the lungs and bones.

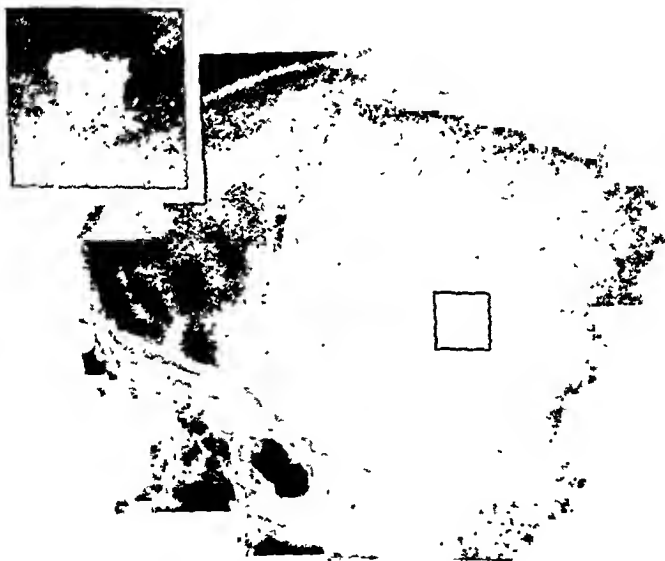


Fig. 5.—Case 3. Solitary calcified tuberculoma.

CASE 3.—H. R., a 9-year-old white boy, sustained a head trauma on Feb. 2, 1948. Following the accident, he vomited twice and developed some drowsiness. The neurological findings on admission were entirely negative. Rapid improvement of the patient's condition permitted an early discharge from the hospital.

Roentgenologic examination of the skull did not disclose any fracture lines or depressed fragments, nor were there signs of increased intracranial pressure. There appeared, however, in the right parietal area, 10 mm. to the right of the midline, an oval shaped serrated calcium deposit measuring 7 by 10 mm. in diameter (Fig. 5). A chest roentgenogram disclosed calcium deposits in the left hilar area and linear densities in the left intermediate lung field resembling pulmonary scars.

At the age of 12 months the patient had been diagnosed as having childhood tuberculosis, on the basis of a chronic pulmonary infiltration, cervical lymphadenopathy, and positive tuberculin tests. His father was known to have active pulmonary tuberculosis at that

time. At the ages of 3 and 5 years, he was known to have had a number of convulsions. Otherwise, his physical and mental development had been satisfactory under the guidance of a tuberculosis clinic. At the time of hospital admission, he was considered to have arrested pulmonary tuberculosis.

Comment.—In a 9-year-old boy, a calcified intracranial mass was recognized roentgenologically as an incidental finding. The history of childhood tuberculosis, as well as the characteristic roentgenologic findings, make it very likely that the observed intracranial calcified mass represents a tuberculoma which was apparently asymptomatic at the time of observation.



Fig. 6.—Post-mortem roentgenogram of brain (Case 1). Note the serrated and angular appearance of the calcified tuberculomas.

ROENTGENOLOGIC FEATURES

Calcified tuberculomas of the brain may vary greatly in size and number. The calcium deposits in these lesions measure usually from a few millimeters to 2 to 3 cm. in diameter.³ Though most of the lesions have been described as solitary, multiple lesions have occurred in a smaller number of cases.² Thus, Borchardt⁵ described the occurrence of four small calcified tuberculomas in a 7-year-old child. The presence of eleven calcified tuberculomas, as observed in Case 1, appears quite unusual in this respect. To my knowledge there is no other proved case in the literature in which such a great number of lesions was detected during life.

A brief consideration of the gross pathologic features of cerebral tuberculomas may explain the radiologic pattern of the individual lesions. The pathologic study of Evans and Courville⁶ revealed that intracranial tuber-

culomas usually contain three distinct zones. The center consists of a structureless caseous core, whereas the outer zone is formed by partially or completely hyalinized connective tissue. At the junction of these layers calcification may take place, with formation of an intermediate calcareous zone surrounding the necrotic focus. This calcareous layer usually becomes indented and fractured as the outer zone of connective tissue shrinks and the necrotic center of the tuberculoma is absorbed or calcified.

On the basis of these pathologic findings, Weinberger and Grant³ analyzed the literature and observed that the calcareous deposits in tuberculomas of the brain will frequently cast a characteristic shadow on roentgenographic examination. The individual calcifications are usually rather homogeneous in their center, but have a serrated, lacelike, angular margin, representing the intermediate calcified zone of the tuberculoma. In those lesions in which the indentation and fragmentation of the calcareous shell are more pronounced, small calcium spicules and plaques seem to be separated from the main center of calcification. The tuberculomas thus lose their originally compact structure, becoming irregular in outline and varying greatly in their various dimensions. These roentgenologic features are illustrated to advantage in a roentgenogram of the brain in Case 1 (Fig. 6). The calcareous lesions disseminated throughout the cerebrum and cerebellum are seen to have a distinctly serrated and angular profile. Several of the larger lesions disclose a very irregular contour, indicating considerable distortion and fragmentation of the calcareous shell.

DIFFERENTIAL DIAGNOSIS

Though the roentgenologic appearance of calcified intracranial tuberculomas is frequently very characteristic, collateral clinical evidence should always be sought in differential diagnosis from other calcified intracranial lesions. It is beyond the scope of this paper to describe in detail the various types of pathologic intracranial calcifications occurring in childhood and their differential diagnosis. In the following paragraphs, some of the more important calcifying intracranial lesions will be briefly discussed.

Among neoplastic conditions, craniopharyngiomas and angiomas deserve foremost consideration. In craniopharyngiomas, the calcification may be flocculent or linear, extending frequently into the pituitary fossa, which is usually enlarged and deformed.¹⁰ Calcification in angiomas assumes a characteristic double contour and is cast into a tortuous and racemose pattern with predilection for the occipital areas of the brain.¹¹ Calcification of subdural hematomas usually consists of linear strands and plaques close to the inner table of the skull.¹² Gliomas in childhood rarely calcify as extensively as tuberculomas except for ependymomas, which would be difficult to differentiate on the basis of roentgenologic observations alone.¹³

In the presence of multiple calcified tuberculomas, several conditions enter the differential diagnosis. Of foremost importance are the cerebral calcifications observed in tuberous sclerosis. In this condition the calcified lesions are usually discrete, smooth in outline, and in close relationship to the ventricular system,¹⁴ though cortical lesions have also been observed in this disease. The differential diagnosis is usually not difficult, if attention is paid to the cutaneous manifes-

tations of this disorder (adenoma sebaceum, cutaneous fibromas, and café au lait spots) and to the mental retardation exhibited by patients with this disease.

Recently, cerebral calcifications due to toxoplasmosis have attracted a great deal of attention.¹² In this protozoan infection, multiple flocculent calcifications usually not more than 2 mm. in diameter are found to be scattered throughout large areas of the brain. In addition, curvilinear calcifications entirely unlike those observed in tuberculoma have been described. The presence of chorioretinitis, hydrocephalus, or microcephalus is a common finding in this condition and is of considerable importance in differential diagnosis.

Among the rarer intracranial calcifications in childhood, symmetrical calcification of the basal ganglia should be mentioned.¹⁵ The calcification in this condition is usually flocculent, though occasionally coalescence of these small densities may occur. The typical location and symmetrical distribution of these lesions, as well as clinical signs of hypoparathyroidism, are important in the establishment of a correct diagnosis. In so-called calcification epilepsy,¹⁶ a large number of small, nodular, smooth calcifications may be disseminated throughout the cerebral cortex. The great number of the lesions, their smooth contour, and familial occurrence should be of aid in differential diagnosis.

CLINICAL CONSIDERATION

The clinical signs and symptoms of tuberculoma are difficult to evaluate in those cases in which tuberculous meningitis overshadows all other clinical features. Rich and McCordock¹⁷ have emphasized that the development of tuberculous meningitis usually can be traced to the rupture of a cortical or meningeal tubercle into the subarachnoid space with subsequent discharge of organisms into the cerebrospinal fluid. Nevertheless, the formation of an intracranial tubercle does not necessarily lead to the immediate development of meningitis, nor will all tuberculomas ultimately take this course.

In those cases in which the intracranial tuberculoma remains isolated, the clinical symptomatology depends largely upon the site of the lesion. Tuberculomas of the cerebrum, because of their predilection for the cortex, are frequently the cause of generalized or jacksonian convulsions. Signs of increased intracranial pressure rarely develop in these cortical lesions since they are usually limited in size. On the contrary, tuberculomas of the cerebellum and brain stem not infrequently cause obstruction of the ventricular system or subarachnoid pathways. Generally, intracranial tuberculomas are difficult to differentiate from other space-occupying intracranial lesions, which is demonstrated by the frequency with which they are removed under the mistaken diagnosis of brain tumor.

Undoubtedly, there is a significant number of patients in whom tuberculomas of the brain may remain temporarily or permanently asymptomatic. This is well illustrated in Case 1 of this paper, in which no cerebral manifestations were apparent up to the time of the terminal illness. It is striking that this extensive disseminated tuberculous process of the brain remained clinically silent for a considerable period of time. This observation emphasizes that in the differential diagnosis of both symptomatic and asymptomatic cerebral calcifications, tuberculomas deserve proper consideration.

SUMMARY AND CONCLUSION

Tuberculomas of the brain are more frequently observed in childhood than in adult life. In a small number of cases calcification of the lesions has been observed.

On roentgenographic examination calcified tuberculomas of the brain have a characteristic serrated and angular appearance which should frequently permit their differentiation from other calcifying intracranial lesions. Calcifying tuberculomas may occur as solitary or multiple lesions in any portion of the brain, rarely measuring more than 3 cm. in diameter.

Three cases of calcified intracranial tuberculomas are presented. In two cases, the lesions were multiple and in one case, solitary. In the first case the roentgenologic observation of multiple calcified cerebral tuberculomas was confirmed on autopsy. In the other two cases the history of active tuberculosis and the characteristic x-ray appearance make the tuberculous nature of the observed intracranial calcifications very likely.

It is conceivable that clinically asymptomatic cerebral tuberculomas occur more frequently than statistics indicate and that these lesions may remain unrecognized in the absence of roentgenologic studies.

Calcified tuberculomas of the brain should always be considered in the differential diagnosis of solitary or multiple, symptomatic or asymptomatic, intracranial calcifications.

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THE TREATMENT OF PNEUMOCOCCAL MENINGITIS WITHOUT INTRATHECAL PENICILLIN

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THE ill effects associated with intrathecal forms of medication in the treatment of meningitis have recurred with each new form of therapy as it has developed. With the use of serum and each of the sulfonamides, the intrathecal route has been first advocated and then discarded. At present, intrathecal penicillin is still generally accepted in the treatment of pneumococcal meningitis, although there are some indications that it is losing favor. Rammelkamp and Keefer⁷ and others^{8, 9} have presented evidence that penicillin given by the intravenous or intramuscular route does not diffuse readily into the cerebrospinal fluid. In experimentally induced pneumococcal meningitis in dogs, systemic penicillin alone proved inferior to systemic and intrathecal administration.¹⁰ However, it has been demonstrated that acute inflammation of the meninges does promote diffusion of the antibiotic into the spinal fluid.¹¹ Reports showing that the intrathecal administration was not without danger^{2, 15, 16} have led us to make limited use of this form of therapy. Subsequently, a few reports of single cases of pneumococcal meningitis treated successfully with intravenous or intramuscular penicillin have appeared.¹²⁻¹⁴ Furthermore, there is a lack of convincing evidence that the introduction of penicillin into the subarachnoid space increases the concentration of the antibiotic in the meningeal tissues. All layers of this tissue are richly supplied with blood vessels or lymphatics or both. Since the infection is one involving the meninges, it would seem logical that the purpose of treatment would be to maintain a high concentration of the therapeutic agent in the tissues and not in the exudate. This can best be effected by adequate blood levels.

It is the purpose of this communication to report seventeen patients with meningitis due to pneumococci treated without intraspinal penicillin, fourteen of whom recovered.

GENERAL OBSERVATIONS

The individuals treated in this series are listed in Table I. Table II shows the distribution of the patients according to the amount of penicillin given and the results of therapy in terms of the percentage of patients who recovered and who suffered complications. Also a group of five individuals who received additional intrathecal medication are included in Table II. The patients ranged in age from 6 weeks to 63 years. Six were below 2 years of age and five were between 2 and 14 years of age. With one exception, all were treated with com-

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bined sulfadiazine and penicillin therapy. Type-specific antipneumococcal serum was not used in any of the patients included in Table I, but it was administered to two of those receiving intrathecal penicillin.

TABLE I. SUMMARY OF SEVENTEEN PATIENTS TREATED WITHOUT INTRATHECAL PENICILLIN

CASE NO., INITIALS, AGE	DURATION OF ILLNESS PRIOR TO ADMISSION (DAYS)	CONDITION ON ADMISSION	SPINAL FLUID NO. CELLS, TYPE PNEU- MOCOCCUS	DURATION OF FEVER IN DAYS IN HOSPITAL	OUTCOME
1. N. M. 52 yr.	1	Comatose T. 103° F.	4,000 I	11	Recovery
2. N. G. 25 yr.	2	Comatose T. 105° F.	25,000 VIII	12	Recovery
3. I. B. 4 mo.	3	Comatose T. 103° F.	15,000 XIX	37	Recovery Brain damage
4. R. B. 3 mo.	14	Lethargic T. 100° F.	624 VII	42	Recovery
5. G. L.* 6 mo.	10	Comatose T. 105° F.	240 I	124	Death in 124 days
6. F. M.* 14 yr.	30	Comatose T. 104° F.	17,300 IV	-	Death in 2 hours
7. E. S.* 8 yr.	14	Irrational T. 104° F.	8,000 III	-	Death in 18 hours
8. D. W. 7 yr.	5	Comatose T. 105° F.	1,600 III	8	Recovery
9. D. L.* 17 yr.	7	Irrational T. 104° F.	9,000 XXVIII	4	Recovery
10. M. L. 2 yr.	14	Comatose T. 104° F.	3,500 XVIII	4	Recovery
11. C. P. 4 yr.	2	Comatose T. 103° F.	2,000 ?	18	Recovery
12. I. S. 3 mo.	1	Moderately ill T. 104° F.	600 IV	17	Recovery
13. E. R. 40 yr.	1	Comatose T. 102° F.	8,000 ?	10	Recovery
14. F. S.* 63 yr.	40	Comatose T. 101° F.	3,000 ?	8	Recovery
15. T. D.* 16 yr.	25	Comatose T. 103° F.	2,600 I	4	Recovery
16. A. G. 4 mo.	5	Comatose T. 105° F.	1,200 VII	22	Recovery Brain damage
17. S. B. 6 wk.	1	Lethargic T. 103° F.	1,000 VII	10	Recovery

*Signifies therapy with sulfonamides and/or penicillin before admission to this hospital.

TABLE II. A COMPARISON OF RESULTS OF COMBINED SULFADIAZINE AND PENICILLIN THERAPY IN PNEUMOCOCCAL MENINGITIS*

GROUP	NO. PATIENTS	AVERAGE DAILY DOSE PENICILLIN (UNITS)	PER CENT RECOVERED	PER CENT COMPLICATIONS
A	10	120,000-160,000	70	10
B	7	320,000-400,000	100	14
A and B (Total of all patients treated with systemic penicillin)	17	120,000-400,000	82	12
C (Patients treated with systemic and intra- theal penicillin)	5	120,100-160,000 I.M. or I.V. 5,000-20,000 intrathecal	80	60

*All but one of the patients received sulfadiazine.

The duration of illness in all patients prior to admission, including those with intrathecal therapy, varied considerably (Table I). Only two patients were referred to this hospital with an established diagnosis of meningitis confirmed by a lumbar puncture before admission. Ten of the patients had evidence of an otitis media for days or weeks before admission, and four had findings of pneumonia at the time they were admitted. Three patients also were proved to have mastoiditis. Only four showed no evidence of a complicating infection at the time they were first seen here or gave no history of such an infection. The time of onset of meningitis in most of these patients is obviously difficult to estimate. This is particularly true in the infants and children. With the exception of one patient, it is probable that meningitis was present in most for only a brief period before the time of admission to this hospital. Fourteen of the patients had received no specific therapy before being seen here. The remaining eight had either sulfonamides, penicillin, or both for varying intervals of time before admission.

BAACTERIOLOGIC STUDIES

Baeteriologic diagnosis was made by smear and culture of the spinal fluid. Cultures were positive in all except one patient, who had positive cultures in another hospital and had organisms seen in the spinal fluid smears on two occasions after admission here. One patient had a positive culture but a negative spinal fluid smear. Pneumococcal typing was done on all but three patients. In most of the patients lumbar punctures were done on admission and again forty-eight hours later, or more frequently as seemed indicated by observation of the individual case. Particular emphasis was placed on the persistence of a positive culture or smear. Routine cell counts, sugar, and protein determinations of the spinal fluid were also made at these times. Blood cultures were taken at the time of admission on five patients, and all were negative.

RESULTS

Fourteen of the seventeen patients treated with systemic penicillin and sulfadiazine recovered from the meningitis, a rate of 82.3 per cent, which compares very favorably with other series reported in the literature.¹⁻⁶ These findings are listed in Table II. Three patients died while on this form of therapy, two within eighteen hours of the time that they were first seen at this hospital. The third patient lived 124 days and at autopsy showed no evidence of active infection. However, there was marked cortical atrophy and degeneration plus internal hydrocephalus. Two of the fourteen patients who recovered had severe mental retardation.

Not one of the patients who responded to therapy had a relapse of the meningitis. To minimize this common occurrence, dosage should be adequate and continued long enough to eradicate completely the quiescent foci of infection. The average duration of therapy in patients who recovered was twelve days after the temperature returned to normal.

A further analysis of the data indicates that regardless of the antecedent type of pneumococcal infection (i.e., otitis media, pneumonia, etc.) the results

of therapy were favorable. Moreover, as shown in Table I, the duration of such illness previous to therapy did not seem to influence the final outcome. Eighty-two per cent of the patients showed some foci of infection other than meningitis. It is interesting to note that the factor of age had little significance prognostically. Deaths were rather evenly distributed over the entire age span, and complete recovery occurred in both the youngest and the oldest patient. However, all patients who had sequelae of brain damage were less than a year of age. The type of pneumococcus did not influence the course of the disease. A similar observation regarding the pneumococcus type has been reported by White and his associates⁶ in a series of fifty patients. No significant prognostic value could be attached to either the sugar or protein content of the spinal fluid with repeated determinations during the course of each illness.

The severity of illness was no greater in the five patients who received the intrathecal penicillin than in the others. Unfortunately, results in this group are not significant because of the small number. There was one death, and three patients had neurological complications. One of the sequelae, a seventh and eighth nerve paralysis, may have been due to the accompanying mastoiditis and mastoidectomy. Nevertheless, the high incidence of complications in this small group plus others reported in the literature associated with intrathecal penicillin^{2, 15, 16} should make one cognizant of the potential danger of this form of therapy. Although it is recognized that no definite proof is given in this series, the impression of a poor effect is obtained.

DISCUSSION

The fact that treatment of pneumococcal meningitis systemically resulted in a recovery rate as good as in reported series where intrathecal therapy was used indicates that the latter, in most instances, is unnecessary. Moreover, as previously mentioned, some ill effects have been observed with intraspinal penicillin. It should be stressed that each patient should be treated individually. Careful observation during the first twenty-four to forty-eight hours of illness with repeated lumbar punctures and bacteriologic examination of the fluids should be an accessory guide to therapy.

No precise statement can be made concerning the dosage of sulfadiazine or penicillin. It should be emphasized that the sulfonamide is as important as the penicillin in the therapeutic program. The average amount of sulfadiazine given to infants and children in the present study was 0.2 Gm. per kilogram of body weight (1.5 gr. per pound) per twenty-four hours. In adults the average doses were 6.0 to 8.0 Gm. per day. No untoward results were encountered though most of the patients were kept on this medication for periods longer than two weeks. The average daily doses of penicillin in Group A, Table II, were 120,000 to 160,000 units intramuscularly. A few patients also received 10,000 to 30,000 units intravenously at the start of therapy. In Group C intrathecal penicillin was given in addition to the systemic injections, in dosages of 10,000 to 15,000 units once or twice a day for an average of four days. In Group B, the dosage of penicillin averaged from 320,000 to 400,000 units intramuscularly daily, and in addition several patients received an initial

100,000 to 200,000 units intravenously. No intrathecal penicillin was used during this latter period (from 1946 to the present), and all seven of the patients recovered (Cases 11-17, Table I). The amounts just specified were used regardless of age and were given at three-hour intervals. In Group A the average duration of therapy was thirty days, and in Group B the average duration of therapy was twenty-two days. In both groups sulfadiazine, as well as penicillin, was given for the entire time in the majority of instances (Table II). Although the number of cases is small, it would seem that the use of larger doses of the antibiotic gave better results than in the earlier cases where smaller amounts were used. Another possible factor contributing to differences in these results may have been the changes in the production of penicillin resulting in a more uniform product, which was administered to the individuals in Group B.

In only one case can it be stated that adjunctive use of intrathecal penicillin may have accomplished more than systemic penicillin alone. This was in the only patient who had persistently positive spinal fluid cultures (for ten consecutive days) until intrathecal penicillin was given. Other factors may have influenced the elimination of the organism from the spinal fluid. Concurrent with the introduction of penicillin into the subarachnoid space, the dose of intramuscular penicillin was increased and antipneumococcal serum was administered. In addition, it was noted on several previous examinations at this hospital that the patient was mentally retarded. Transillumination of the head showed a marked defect of intracranial structures in the frontal regions. What effect, if any, the intracranial anomaly had upon the course of the disease is difficult or impossible to evaluate. All other patients had negative spinal fluid cultures and smears of the fluid sediments within forty-eight hours of the time that specific therapy was instituted. In one patient treated without intrathecal penicillin, in whom more frequent lumbar punctures were done, the spinal fluid culture became negative in six hours.

SUMMARY

The treatment of seventeen patients with pneumococcal meningitis with sulfadiazine and penicillin resulted in a recovery rate of 82 per cent. No intrathecal penicillin was used in this group. Seven were treated with relatively large doses of penicillin (320,000 to 400,000 units daily) with a recovery rate of 100 per cent.

The therapy of pneumococcal meningitis should be individualized for each patient, and intrathecal penicillin should be reserved for those who do not respond to adequate systemic therapy.

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Addendum

Since the preparation of this manuscript we have treated one other patient with pneumococcal meningitis as outlined above without intrathecal penicillin. She was an infant 10 months of age and recovery was apparently complete.

MORTALITY OF ACUTE INFANTILE DIARRHEA AT THE LOUISVILLE GENERAL HOSPITAL FROM 1943 TO 1947

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IN 1944 Glaser and Bruce¹ reported 180 cases of diarrhea seen at the Louisville General Hospital during the months of July, August, and September from 1940 to 1942. There were thirty-two deaths, or a mortality rate of 17.8 per cent. In 1942 they had fifty-eight cases during these three months with six deaths, or a death rate of 10.3 per cent. The reduction in the mortality rate was believed to be due to certain changes in therapy. Since 1942 we have admitted 570 infants with acute diarrhea to the Louisville General Hospital. Sixty-two of these patients died. The death rate was 10.9 per cent. Although the plan of treatment has changed very little, there has been a marked variation in the fatality rate from one month to the next, and from one year to another. For example, in 1943, during the month of October, there was an 8 per cent mortality, while in November of the same year, there were no deaths. In 1943 the death rate was 13.9 per cent, and in 1944 it was only 4.6 per cent. Because of the different severity of diarrhea during certain months or years, it is very difficult to evaluate properly any plan of therapy unless a control group is available at the same time the new treatment is being used.

In 1943 the majority of the infants were treated as described in the report of Glaser and Bruce. This consisted of starvation for twelve hours in moderately severe cases and for as long as thirty-six hours in the very severe cases. During this period, sips of boiled water were sometimes given. A continuous intravenous drip was begun at the onset of treatment. One-sixth molar sodium lactate was usually given immediately, followed by 5 per cent glucose in saline. Not more than half of the total daily fluid contained saline. At least three ounces of fluid per pound of body weight were given intravenously each day of the starvation period. On the second day of treatment, plasma or blood was often given. Whenever possible, a needle was inserted into a vein without "cutting down," but in most instances of severe diarrhea, it was necessary to cannulate the vein.

If the patient improved after twelve to thirty-six hours, he was offered buttermilk every three or four hours, and was allowed to take as much of this milk as desired. In those patients who refused buttermilk, boiled skimmed milk was given. When the diarrhea ceased, the feeding was gradually changed to a whole milk or an evaporated milk formula.

Nearly all infants received either sulfathiazole or sulfadiazine in a daily dosage of one grain to one and one-half grains per pound of body weight. This

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was usually administered subcutaneously in a 5 per cent solution during the period of starvation, after which the medication was given by mouth. A few patients received sulfaguanidine.

In 1944 treatment remained much the same as previously described, except that the infants were started on a small amount of buttermilk and this gradually increased.

During 1945 and 1946 longer periods of starvation were employed, and in severe cases, intravenous fluid was given for forty-eight or seventy-two hours. In patients with recurrence of diarrhea, starvation was repeated. Greater attention was also given to the administration of plasma to provide needed protein. Except for a few patients who received lactate Ringer's solution, no fluid containing potassium² was given.

Buttermilk, boiled skimmed milk, or Protein milk was used in small amounts after the period of starvation. The milk was gradually increased, and before discharge, the patient usually was on an evaporated milk or a whole milk formula.

The intern and resident staff performed all treatments. Only patients who had not responded to outpatient care or those who were dehydrated when first seen were admitted to the ward. No newborn infants were included in this report, except eight premature infants who were admitted in 1946. The chief complaint in all cases was diarrhea, but about 5 per cent of the patients had some other evidence of infection. Bronchopneumonia and otitis media were most common.

TABLE I. MORTALITY RATE IN ACUTE DIARRHEA 1943 THROUGH 1946

YEAR	NO. CASES	NO. DEATHS	MORTALITY RATE (%)	CORRECTED MOR- TALITY RATE (%)
1943	201	28	13.9	11.2
1944	87	4	4.6	4.6
1945	136	14	10.3	8.3
1946	146	16	11.0	3.7
Total	570	62	10.9	7.5

The mortality rates are shown in Table I. The highest death rate, 13.9 per cent, occurred in 1943, although the treatment was the same as that given in 1942. During July, August, and September, 16.2 per cent died in 1943, while the fatality rate was 19.3 per cent during the same months in 1942. The lowest fatality rate was found in 1944 when only 4.6 per cent died. During July, August, and September of that year the death rate was 10.2 per cent. Fewer cases occurred during that year, and since only minor changes in therapy were instituted, it seems justifiable to conclude that the disease was of less severity than usually encountered.

The "corrected mortality" given in Table I was calculated with omission of those patients who died within the first twelve hours. In 1946 there were four patients who died within two hours after admission, giving a corrected mortality rate of 9.1 per cent. During 1946 eight premature infants were transferred from a premature station in which an epidemic of diarrhea was present. The mortality rate had been over 90 per cent at this premature nursery, and we were able to save only one of the eight. Because of the recognized high

mortality rate of epidemic diarrhea in premature infants, the "corrected mortality" of 3.7 per cent was calculated by omitting these eight infants.

During this four-year period, there were 447 white infants with forty-seven deaths, giving a mortality rate of 10.5 per cent. There were 123 Negro infants with fifteen deaths, or a death rate of 12.2 per cent.

The mortality rate according to age is shown in Table II. In general, the younger the infants, the higher the death rate. Fifty per cent of the infants who died were under 4 months of age. Likewise, the smaller the infants at time of admission, the higher the fatality rate. Forty-eight per cent of the infants who died weighed less than 8 pounds. There was a definite seasonal incidence encountered, and 64 per cent of the cases occurred during the months of July, August, September, and October. The mortality rates during July and August were no higher than the average, but in September and October the fatality rate was 15.4 per cent and 14.3 per cent respectively, as compared to the average rate of 10.9 per cent.

TABLE II. MORTALITY RATE ACCORDING TO AGE

AGE (MONTHS)	NO. CASES	NO. DEATHS	MORTALITY RATE
0-3	190	31	16.3%
4-6	126	15	11.9%
7-12	118	7	5.9%
13-up	136	9	6.6%

The milk that the infant was receiving at the time of the onset of diarrhea seemed to influence the prognosis. Although a good number of the infants were nursing the breast at the time of admission to the hospital, none of these infants died. There was not a single death in four years of an infant who developed diarrhea while nursing the breast.

At least three stool cultures were obtained from all patients except those who died shortly after admission. Among the 570 cases there were only three patients from whom the cultures were positive for dysentery organisms, and these belonged to the Flexner group. *Bacillus typhosus* was isolated from the stools of two infants admitted because of severe diarrhea. Both patients with typhoid recovered, but one patient with dysentery died. Despite the use of rectal swabs and efforts to inoculate the culture plates immediately, the number of positive stool cultures remained surprisingly small.

Weihl and his associates³ have recently reported on the mortality rate of infants with acute diarrhea seen at the Cincinnati General Hospital during the years 1944 and 1945. There were 292 patients with a total of twenty-two deaths. The combined fatality rate for the two-year period was 7.5 per cent. The corrected mortality rate was 5.6 per cent. Because of the similar climate and sectional location of Louisville, it was of interest to compare these mortality rates with those obtained here during the same period. In our series there were 233 cases with 18 deaths in 1944 and 1945. The mortality rate was 8.1 per cent, and the corrected mortality rate was 5.8 per cent.

SUMMARY

The mortality rate of acute diarrhea of infants varies greatly during different months or years.

From 1943 through 1946, 570 patients with severe acute infantile diarrhea were admitted to the Louisville General Hospital. Sixty-two of the patients died. The death rate was 10.92 per cent, and the corrected mortality rate was 7.5 per cent.

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Case Reports

IDIOPATHIC HYPOPARATHYROIDISM

A CASE SIMULATING EPILEPSY AND BRAIN TUMOR

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IDIOPATHIC hypoparathyroidism is a known clinical entity.⁴ The criteria for diagnosis are: (A) low serum calcium level; (B) high serum inorganic phosphorus level; (C) normal skeleton as demonstrated by roentgenography; (D) absence of all signs of renal insufficiency. In many patients, the cause of hypoparathyroidism is obvious, such as inadvertent extirpation of the parathyroid glands following thyroidectomy. In other patients, the cause of the hypoparathyroidism is often very obscure. In these cases, the term "idiopathic" hypoparathyroidism is used. Reports on the pathologic changes of this entity are meager. Yanase⁵ reported hemorrhages in the parathyroids of infants, presumably secondary to birth trauma or neonatal asphyxia. Such injuries often resulted in the hypoplastic glands which were found later in life. The hemorrhages ranged from slight extravasations of blood to massive infiltrations; some of the patients manifested tetany, others did not. Drake¹ reported a ease in which the parathyroids were completely replaced by fatty tissue. He also referred to acute infections as the possible etiologic agents⁶ of the degeneration of parathyroid tissues. It is interesting to speculate upon the role of the severe infection in relation to the subsequent development of parathyroid disease. Acute infection was responsible for the first hospital admission of our patient; however, no specific predominating pathogen was demonstrated upon that admission. Drake¹ found no particular sex incidence in hypoparathyroidism, but noted that most patients reported fall into two age groups, childhood and middle life, very few cases being seen in adolescence or early adulthood.

Another factor which must be considered is that in some cases the symptoms, signs, and laboratory findings of hypoparathyroidism occur because of the lack of secretion of the parathyroid hormone, while in other cases, the patient may be able to produce parathyroid hormone, but the peripheral tissues of the body are unable to respond to this secretion. In such patients the symptoms, signs, and laboratory findings are identical with those found in patients in whom there is lack of production of the hormone. To differentiate the "true" idiopathic hypoparathyroidism—i.e., the condition in which no hormone is produced—from the "pseudo" hypoparathyroidism—i.e., the entity in which the peripheral tissues do not respond to the stimulus of the hormone—the Ellsworth-Howard test is used.⁴ In this determination, parathyroid extract is injected intravenously and the response noted. The primary response is an increased urinary excretion of inorganic phosphorus associated with a lowering of the blood serum inorganic phosphorus and a rise in the blood serum calcium level. If the patient responds to the test by an increased urinary excretion of inorganic phosphorus, then the peripheral tissues are sensitive to the stimulus of the hormone and the disease is due to a deficiency in the elaboration of the hormone rather than to the inability of the body tissues to respond when it is present.

From the service of Dr. Harry S. Altman, pediatrician-in-chief, Lincoln Hospital.

The fact that true idiopathic hypoparathyroidism may simulate epilepsy or even brain tumor is not generally realized. Many of the standard works on neurology do not mention hypoparathyroidism in the differential diagnosis of epilepsy. Shelling,² however, in his book on the parathyroid gland stresses that (1) tetany of parathyroid origin must be differentiated from tetany due to other causes; and (2) tetany must be distinguished from epilepsy. The clinical signs in both syndromes are so very similar that even the most careful observer may readily mistake tetany for epilepsy and vice versa unless analysis of the serum calcium and phosphorus levels is made. Sutphin, Albright, and McCune³ state that there have been three cases at the Massachusetts General Hospital which were diagnosed as idiopathic epilepsy and the patients followed for a period of years before the diagnosis of hypoparathyroidism was finally made by blood chemistry. In the same article, they report a patient with idiopathic hypoparathyroidism who was admitted to the hospital with signs of increased intracranial pressure, choked discs, and convulsive seizures. A cerebral neoplasm was suspected, but electroencephalograms and ventriculograms were normal. Following adequate therapy for the hypoparathyroidism, the papilledema disappeared. This increase in intracranial pressure occurring in hypoparathyroidism may readily simulate brain tumor or other expanding intracranial lesions and may easily mislead the clinician unless a serum calcium determination is made. The physiopathologic mechanism of the increase in intracranial pressure and papilledema is at present obscure. The importance of being aware of the similarity of cerebral neoplasm, epilepsy, and hypoparathyroidism has been mentioned by Levy,⁷ who states: "This patient was in the paradoxical position of knowing what was producing her seizures, but because her symptoms did not fit in with the usual picture of tetany, she was labeled hysterical or epileptic."

The following case of idiopathic hypoparathyroidism is being reported because of its simulation, at various times, of both epilepsy and cerebral neoplasm.

CASE REPORT

E. R. was born of Puerto Rican parentage at the Lincoln Hospital on March 8, 1940. His mother was serologically negative, and delivery was spontaneous and normal. His neonatal period, growth, and development were apparently normal. The family history was noncontributory.

His first Lincoln Hospital admission was on Oct. 6, 1941 for severe acute tonsillitis, sinusitis, and erythema multiforme. A suggestive rachitic rosary noted on physical examination was not confirmed by x-ray studies. An electrocardiogram was normal. (See Table I, *a* for blood chemistry.) He was discharged Dec. 14, 1941.

The second admission was on Feb. 17, 1945, at the age of 5 years. Due to poor economic conditions at home the child had been placed in a children's shelter. Three days before release from this institution, he developed a fever, and the night before admission he complained of pain in the right calf, and a lump was noted in that area. He then developed pain in both hands, which was followed by spastic contracture of both hands and wrists. Physical examination on admission revealed a typical carpopedal spasm and positive Chvostek and Trousseau signs. Both of these signs were immediately relieved by administration of 10 c.c. of calcium gluconate intravenously. Laboratory studies revealed a normal blood cell picture and hemoglobin, normal urine, and negative serology. No pathologic change was seen in x-rays of the chest and long bones. The Mantoux test was negative. The chemical study of the blood is shown in Table I, *b*. The child was given calcium gluconate and water-soluble vitamin D preparation orally. He became a diphtheria carrier and was transferred to a contagion hospital.

TABLE I. BLOOD CHEMISTRY DETERMINATIONS

DATE	CALCIUM (MG. %)	INORGANIC PHOSPHATE (MG. %)	ALKALINE PHOSPHATASE (BODANSKY UNITS)	TOTAL PROTEIN (GM. %)	ALBUMIN (GM. %)	GLOBULIN (GM. %)	UREA NITROGEN (MG. %)	CO ₂ COMBINING POWER (VOL. %)	CHOLESTEROL (MG. %)	CEPHALIN FLOCCULATION
<i>First admission</i>										
a. Oct. 20, 1941	10.4		7.0	5.3	3.6	1.7	12.0			
<i>Second admission</i>										
b. Feb. 18, 1945	6.6	7.8	8.1	7.2	4.7	2.5	13.0	48		
<i>Interval during which no vitamin D was given</i>										
<i>Third admission</i>										
c. Oct. 23, 1945	6.8	7.1	13.2	7.4	4.1	3.3	14.5		205.0	Neg.
<i>5,000 units of vitamin D and 1.5 Gm. calcium chloride given daily</i>										
d. Dec. 5, 1945	7.2	5.7	4.8						178.0	Neg.
e. Dec. 13, 1945	12.2	6.0	6.1							
f. Dec. 26, 1945	11.5	4.5	3.2							
<i>Calcium chloride omitted</i>										
g. Jan. 7, 1946	10.2	3.0	11.2							Neg.
<i>Medication not taken regularly</i>										
<i>Fourth admission</i>										
h. April 22, 1946		11.1	3.4							
i. April 26, 1946	7.8									
j. May 10, 1946	7.0			7.4			14.7		247.0	
k. Sept. 12, 1946	9.3	3.9								
l. Oct. 28, 1946	7.4									
<i>Stabilization on oral calcium gluconate, vitamin D, and dihydrotachysterol</i>										
<i>Fifth admission</i>										
m. March 15, 1948	8.6	4.5	6.0	7.0	4.4	2.6	16.0		182.0	Neg.
<i>Glucose Tolerance Test (mg. %)</i>										
DATE	FASTING	½ HR.	1 HR.	2 HR.	3 HR.	4 HR.				
Oct. 15, 1945	73	84	91	71	66	66				

He was seen for the third time eight months later on Sept. 21, 1945. Thrice during the preceding week the child had had episodes of syncope and unconsciousness, each of about ten minutes' duration, which occurred while he was playing in the street. There were no associated convulsions. No vitamin D preparations had been given during this eight-month interval. Physical examination on admission was essentially normal. There was no sensitivity manifested to carotid sinus pressure. Laboratory studies showed normal blood count, serology, urinalysis, electrocardiogram, and x-rays of skull, chest, and long bones. The blood chemistry determination is shown in Table I. c. Results of the Ellsworth-Howard test are shown in Table II. This test confirmed the diagnosis of true idiopathic hypoparathyroidism. The ophthalmologist found no retinal abnormalities or cataracts. A glucose tolerance test was done on Oct. 15, 1945 (see foot of Table I).

While in the hospital, the patient was observed by a number of investigators to have "seizures," which occurred as many as six times in one day. These episodes occurred while the child was sitting at rest or playing in bed, and on several occasions they seemed to be directly precipitated by the overbreathing associated with emotional excitement. The patient would suddenly be seized with a clonic contraction of the right upper and lower extremities and a twitching of the entire right side of the face; a few seconds later he would show slight cyanosis of the lips; and then after a lapse of from thirty to sixty seconds the

attack would terminate, and he would sink to the bed exhausted. There was a considerable degree of clouding of consciousness during an attack, but the child could apparently hear questions that were put to him during the seizure and would answer them at its termination. He felt "sleepy" after an attack, but there were no residual neurological signs or other symptoms. A consultant endocrinologist believed these episodes to be attacks of petit mal epilepsy complicating an underlying idiopathic hypoparathyroidism. An electroencephalogram was done, the patient's cooperation being exemplary; this revealed an electrical pattern normal for the child's age.

Accordingly, it was postulated that the epileptiform manifestations were a sequel of the underlying endocrine dysfunction, and a therapeutic trial of the oral administration of 50,000 units of vitamin D and 1.5 Gm. of calcium chloride daily was begun on Nov. 28, 1945. On Dec. 5, 1945, blood chemistry determinations were done. (See Table I, *d*.) On December 13, the values were as shown in Table I, *e*, on December 26, as shown in Table I, *f*. On December 29, the calcium chloride was omitted from the therapeutic regimen. On Jan. 7, 1946 the levels were as seen in Table I, *g*. After the onset of therapy on Nov. 28, 1945, the patient did not have a single epileptiform manifestation of any description, and appeared to be normal in all his activities. On Jan. 15, 1946, a program was begun to reduce the vitamin D dosage gradually to a minimum daily requirement sufficient to prevent any epileptiform episodes. However, the child failed to appear at the follow-up clinic.

The patient again came under medical observation on April 22, 1946. He was admitted to another hospital because while at home he developed carpopedal spasm and laryngeal stridor. These signs were seen on admission, and twitchings of the face and rigidity of the muscles of the neck and abdominal wall were also present. A purulent drainage from a perforated right ear drum was noted. The child appeared acutely ill and was in a moderate state of anxiety. Medication had not been taken regularly during the interval between hospitalizations.

Laboratory work-up on admission revealed a mild polymorphonuclear leucocytosis and a normal urine. Serologic and tuberculin tests were negative. Serum calcium determination was not done on admission, but the other chemistry determinations performed during this fourth hospitalization are shown in Table I, *h*, *i*, *j*, *k*, and *l*. The basal metabolic rate was plus 4. Electrocardiograms taken before and after intravenous injection of calcium gluconate were normal. X-rays of the skull and long bones showed no abnormalities. An electroencephalogram taken fifteen days after admission showed an electrical dis-

TABLE II. ELLSWORTH-HOWARD TEST

DATE	TIME	VOLUME OF URINE EXCRETED (C.C.)	TOTAL INORGANIC PHOSPHORUS CONTENT (MG.)	SERUM CALCIUM (MG. %)	SERUM INORGANIC PHOSPHORUS (MG. %)
Oct. 28, 1945	9-10 A.M.	26	23.4	7.0	7.1
	10 A.M.—2 c.c. of parathyroid extract intravenously				
	10-11 A.M.	34	51.0	--	--
	11-12 N	39	90.0	--	--
	12 N-1 P.M.	15	34.0	8.0	6.0
June 10, 1946	7 A.M.	50	35.5		
	8 A.M.	20	11.4		
	10:05 A.M.	150	33.3		
	10:15 A.M.—2 c.c. of parathyroid extract intravenously				
	10:20 A.M.	200	--		
	11:20 A.M.	12	136.0		
	1:20 P.M.	4	26.0		
	2:15 P.M.	85	15.6		

charge rate slightly slower than that of the average subject of the patient's age. A Stanford-Binet test, despite language difficulties, showed an intelligence quotient of 92. Dental x-rays showed malocclusion of the teeth but otherwise were unremarkable. No nail changes were noted at this time.

On May 1, 1946, examination of the optic fundi was not remarkable, but on May 15, 1946, the optic discs were noted to be elevated and the retinal vessels tortuous. These findings remained the same for the duration of hospitalization. A lumbar puncture performed on May 21, 1946, with the child struggling moderately, showed a pressure of 210 mm. of water, the fluid being otherwise normal. A visual field examination was done on May 30, 1946, and a constriction of from five to ten degrees in all meridians was found. An Ellsworth-Howard test was done on June 10, 1946 (Table II); again the diagnosis of idiopathic hypoparathyroidism was confirmed. The neurological staff consultants felt that to rule out a cerebral neoplasm a ventriculogram was indicated, which was done on Sept. 27, 1946, after the patient had had normal serum calcium levels for a period of over two months with no changes seen in the degree of papilledema. The ventriculograms were normal. Another lumbar puncture was done following ventriculography with the aid of 0.2 Gm. of nembutal, and the pressure was 150 mm. of water. On admission the child's tetany had been treated with 10 c.c. of calcium gluconate intravenously, and then he was placed on oral calcium and vitamin D preparations for the rest of his hospital stay. He was finally stabilized on a regimen of oral calcium gluconate, vitamin D, and dihydrotachysterol; this served to maintain his serum calcium at levels above 9.0 mg. per cent. The purulent otitis media had cleared while the patient was in the hospital, and he was discharged on Nov. 18, 1946. The final diagnosis was true idiopathic hypoparathyroidism and bilateral papilledema.



Fig. 1—Showing advanced degree of koilonychia.

The patient again came under our observation on March 8, 1948. Since his hospitalization in November, 1946, he had been receiving daily doses of oral calcium gluconate, vitamin D, and dihydrotachysterol. He had been apparently normal in all respects, had had no seizures of any description whatsoever, and

was an honor student in his class at school. However, during the past six months he had begun to develop changes in his fingernails. Physical examination on this last visit revealed an advanced degree of koilonychia or "spooning" of the fingernails; the left great toenail was also affected. (See Fig. 1.) Koilonychia is one of the trophic disturbances of the ectoderm that may occur in chronic hypoparathyroidism. However, we were not able to demonstrate the presence of monilia organisms here, in contrast to the cases reported by Sutphin and his associates.³ The skin of the body was normal in all respects. The optic fundi were normal. The teeth were also normal. The patient was now 8 years old, weighed 50 pounds, and was 45½ inches tall. The blood count was normal. Urine and serology were normal. The blood chemistry is shown in Table I, *m*. X-rays of the skull, chest, and long bones revealed no abnormalities. An electroencephalogram was entirely normal for the patient's age.

DISCUSSION

This case clearly illustrates the difficulty in distinguishing epilepsy and brain tumor from hypoparathyroidism. The only way by which the diagnosis of hypoparathyroidism can be made is by determination of the serum calcium and phosphorus levels. In view of the differences in therapy for the three conditions, it is essential that a correct diagnosis be made. We are of the opinion that before any person is labeled as an epileptic or operated upon for a brain tumor, a serum calcium and phosphorus determination should be performed. It is only by this simple procedure that hypoparathyroidism can be diagnosed, particularly in childhood.

SUMMARY

1. The literature has been reviewed with emphasis on the clinical aspects that may at times be common to the conditions of epilepsy, brain tumor (or other expanding intracranial lesions), and hypoparathyroidism. The last-mentioned state may be readily differentiated by serum inorganic phosphorus and calcium determinations.

2. A case of idiopathic hypoparathyroidism is reported which illustrates the resemblance among these three conditions.

We are indebted to Miss Fanya Woll for her cooperation in the blood chemistry studies.

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CONGENITAL FOLLICULOPUSTULAR ERUPTION

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INTRODUCTION

CONGENITAL pustular eruption appears to be a very rare condition, and its relation to congenital impetigo (congenital pemphigus neonatorum) is a controversial subject. It therefore seems justifiable to report the following case where a widespread folliculopustular eruption occurred in an infant delivered by cesarean section and where staphylococci were found on direct examination and by culture.

CASE REPORT

On Oct. 6, 1947, Mrs. F. K., age 33, was admitted to the hospital for an elective cesarean section. She was not in labor, and her membranes were intact. Her expected date of delivery was October 30. She had had three previous cesarean sections because a pelvic deformity resulting from poliomyelitis in childhood prevented normal delivery. She had felt exceptionally well during her pregnancy except for a "head cold" two weeks before admission. She had no disease of the skin. Her serologic test for syphilis was negative. At the time of entry into the hospital, blood and urine studies were normal. Her temperature was normal. At 8:20 A.M. Oct. 7, 1947, she was delivered by cesarean section of a male infant weighing 6 pounds, 11 ounces. The surgeon handed the infant to an assistant who aspirated the mucus and tied the cord. Abnormalities were not looked for at that time and none was observed. The infant was wrapped in a blanket, put in a basket, and removed to the nursery. While cleaning the infant a pustular eruption was observed. At this time the baby was less than 40 minutes old.

Scattered folliculopustular lesions were noted on the pubis, perineum, buttocks, thighs, axilla, shoulders, neck, chin, and scalp. The lesions were largest on the lower portion of the trunk (Figs. 1 and 2). These pustules were 6 mm. in diameter, tense, dome-shaped, and pierced by a central hair. Their bright yellow color stood out in sharp contrast to the background of normal newborn erythema. The lesions elsewhere on the body were smaller, diminishing to pin-head-size or less. Rupture of the larger lesions produced a thick, heavy, creamy pus. Smears of this purulent material revealed many gram-positive cocci in clumps. Staphylococcus colonies were obtained on culture. These were almost nonchromogenic and on primary isolation were tentatively called type albus. They were coagulase-negative when first isolated, but on serial transfer on special media they eventually produced more pigment and became weakly coagulase-positive.

Because building alterations were in progress, the infant had to be "isolated" in a corner of the general nursery. After smears and cultures were obtained the lesions were opened and painted with one per cent aqueous solution of gentian violet. Penicillin therapy, 10,000 units five times a day, was started. With this treatment the lesions readily subsided without crusting. Penicillin was stopped after two days, and an antiseptic powder was the only therapy employed. However, on the sixth day a few more lesions appeared in the groin. At

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this time the baby was moved to another floor. Ten thousand units of penicillin were given once a day, and gentian violet was applied locally. By the eighth day there was an apparent increase in the number of pustules. Therefore, the dose of penicillin was increased to 10,000 units every three hours for the next three days. This finally produced a complete regression of all lesions.

Aside from the skin eruption, the infant's progress was normal. He took his formula well and otherwise appeared healthy and comfortable. At no time during his hospital stay did his temperature rise above normal. Routine urinalyses on four occasions were negative. He was discharged on the seventeenth day.

The mother's postoperative course was uneventful. Her temperature remained at normal levels, and she was discharged on the eleventh postoperative day.

As mentioned previously, the infant was allowed to remain in the general nursery. His bassinette was set aside in one corner. A sterile gown and antiseptic solutions for bathing the hands were provided for anyone who handled him. Within one week fourteen cases of a similar eruption appeared among the newborn infants. All lesions were of the folliculopustular type, but smaller than in the original case. There were no bullous or vesicular lesions. Only the first three cases of this epidemic were cultured. In all three, pure cultures of *Staphylococcus aureus* were obtained. These strains were all coagulase-positive.



Fig. 1.



Fig. 2.

REVIEW OF THE LITERATURE

Congenital bullous impetigo is of rare occurrence. However, sporadic cases have been reported throughout the literature. This phase of the subject was first reviewed by Labardt and Wallart¹ in 1908 and later further reviewed and supplemented by Reed,² Freeman,³ and others. An infant with congenital bullous impetigo delivered by cesarean section has been reported by Weston.⁴ A review of the literature indicates that congenital exanthemas are next in order of rarity, and that a congenital pustular eruption is the most unusual of all. Certainly, reported cases of pure pustular eruptions, other than smallpox, occurring congenitally, are exceedingly few in number.

In 1928 Reed² reported a case of an infant born with a pustular eruption on the scrotum from which *Streptococcus hemolyticus* was cultured. The infant subsequently developed small pemphigoid blebs and a subdermal fluctuant mass on the scalp. All lesions subsided uneventfully. In 1931 Jordan⁵ reported the case of an infant who showed many pustules at birth. On the sixth day of life an abscess developed in the left breast from which *Staph. aureus* was cultured.

The baby finally succumbed to an abscess of the scalp and a cellulitis of the neck on the seventeenth day. At wide variance with the conclusion of extreme rarity of this condition is Parmelee's⁶ statement that he has observed six to eight cases of congenital pustules each year among the newborn infants at Cook County Hospital. Cultures taken in about ten instances were negative. In answer to an inquiry⁷ Parmelee stated that the cases of which he spoke were similar in appearance to ours as shown in Figs. 1 and 2. Hence a revision of opinion may be in order. Apparently many cases of congenital pustular eruption have gone unreported in the past, and the condition, while still unusual, may not be as extremely rare as the paucity of available reports would indicate.

DISCUSSION

Most of the cases reported in the literature under the title "congenital pemphigus neonatorum" are of the bullous type. A few showed pustules and bullae mixed, while wholly pustular eruptions are the least common. These differences in the clinical picture long ago raised the question of classification. Reed² was of the opinion that his case of congenital pustular eruption represented a variant of congenital impetigo. He therefore proposed the name "pyodermatitis neonatorum" to encompass all pyogenic skin infections occurring congenitally or appearing in the newborn infant. Irgang and Alexander⁸ later objected to Reed's comprehensive designation and defined as an entity a superficial pustular folliculitis which they observed in the newborn period. All their patients were normal at birth, the eruption first appearing during the early days of life. Cultures were done in only one instance, and *Staphylococcus albus* was obtained. The case reported herein is clinically similar to those described by Irgang and Alexander. Certainly the lesions in no way resembled those of a bullous impetigo, and it would be improper to designate the case as such. The bullous, pustular, and mixed varieties are in all probability alike in that each has its origin in an infectious agent. Their differences are probably due to variations in the strains of the causative organisms and their virulence, site of implantation, and other factors.

The question of the mode of transmission of the infectious agent from the mother to the fetus can only be speculated upon. Matzenauer,⁹ Gilner and Nelson,¹⁰ and others have postulated a transplacental route. Such an assumption infers a hematogenous infection in the mother. However, most of the mothers in reported cases were apparently well or had some trivial antecedent infection. Blood cultures, where done, were in most instances negative. If then a blood stream infection were present, it must certainly be mild and transient. That such a situation can exist is possible when it is remembered that not every organism introduced into the blood stream necessarily produces a septicemia. The quantity of bacteria introduced and the virulence chiefly determine the outcome. The circulating phagocytes and the fixed phagocytic cells (reticuloendothelial system) are continually aborting attempts at systemic infection. Yet it may be reasonable to assume that some organisms may escape such defense mechanisms in both mother and fetus and set up an infection in the latter. Still one other point needs explaining. Many of these infections appear so superficial that it seems probable that the infecting agent reached the fetal skin from without and not from within. This infers an infected amniotic fluid. Transfer of bacteria by direct passage through the fetal membranes, as, for example, from an infected cervix, may possibly occur. A transplacental spread to the fetus and thence to the amniotic fluid via the fetal urine is another surmised possibility.

The virulence of organisms causing congenital cutaneous infections (bullous, pustular, and mixed) apparently varies widely. In several instances the original superficial infection has become widespread or involved deeper tissues to pro-

duce death. The mortality percentage probably coincides with that given by Swendson and Lee¹¹ (20 to 50 per cent) for some past epidemics of pemphigus neonatorum before the advent of the sulfonamides and antibiotics. In other cases the process has been self-limited, and simple soap and water bathing has been the only treatment employed. Cultures of various organisms have been obtained. However, not all attempts at culture have been successful. Parmelee,⁶ after his failure to culture organisms in congenital pustules, was inclined to believe that a nonbacterial irritant was at fault. Another explanation is that a self-sterilization process has overcome an infection of low virulence.

The role of an infectious agent in the case reported here is substantiated, but admittedly not proved, by the epidemic of clinically similar lesions following the introduction of the infant into the general nursery. It may be argued that the causal relationship is disproved by the difference in the strains of staphylococci isolated in the original and subsequent cases. However, this apparent discrepancy may be explained in two ways. A variety of staphylococci may have been present in the original case. Baerthlein,¹² as quoted by Reed,² was able to isolate four distinct types of staphylococci from a single bleb. On the other hand, the original staphylococci on repeated transfer on favorable media slowly became more chromogenic and coagulase-positive. Our bacteriologist (Dr. J. B. Miale) holds the opinion that the original strain of apparently weak pathogenicity was able to assume all the features of the typical pathogenic aureus variant when it grew on new and perhaps more favorable soil in the other three infants.

Freeman³ suggested that unnoticed congenitally infected infants, placed in the general nursery, may be one source of origin of epidemics of impetigo neonatorum. The course of events in the present case tends to support such a theory.

The delay in discovering the eruption in the patient presented raises the question of whether the lesions were actually present at birth. Unfortunately, that question cannot be answered with finality. However, the clinical appearance of the lesions (size, various developmental stages, and thick, creamy contents) along with past experimental evidence makes it highly improbable that they developed within forty minutes. Dohi and Dohi,¹³ in experimental inoculation of the human skin with staphylococci, produced erythema in several hours, but pinhead-sized vesicles were evident only after twelve hours. Epstein¹⁴ inoculated human skin with both pure cultures of *Staph. aureus* and material from crusts of staphylococcal impetigo. Small blisters were produced in three and four days respectively.

SUMMARY

A case of congenital folliculopustular eruption occurring in an infant delivered by cesarean section is reported.

Clumped cocci were seen on direct smears taken from the lesions, and staphylococci were cultured.

An epidemic of clinically similar but less extensive cases developed following the introduction of this infant into the general nursery.

The literature on congenital pustular eruptions is reviewed.

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Medical Care

SURGICAL INDICATIONS IN GENITOURINARY TRACT INFECTIONS

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THE purpose of this paper is to offer our present concept of pediatric urologic problems, based upon twenty-five years of experience in the management of urologic problems of children in the St. Louis Children's Hospital. It is hoped that the material presented will be of assistance in the orientation of methods available for the study of urologic problems in children.

Restriction of the subject to infections of the genitourinary tract and their surgical approach necessarily limits the scope of the material which is covered, yet it should be noted that infection of some sort is associated with most urologic disturbances of children. Therefore, the prevention or elimination of infection is of frequent concern to both the pediatrician and the urologist in a great many urologic problems.

EXAMINATION

Urinalysis.—Urinary tract infections in infants and children which require urologic investigation and surgery constitute about one-tenth of those which are encountered. The remaining 90 per cent, predominantly pyelitis or pyelonephritis, respond to chemotherapy sufficiently well to render urologic study unnecessary unless repeated recurrences take place. An experienced observer can almost sense the child with an abnormality or defect in his genitourinary structures in which an associated infection has occurred, by the history of the illness and the child's appearance. Malnutrition and a history of long-standing or repeated urinary infections are the rule.

The investigation of a child suspected of having a surgical infection in the urinary tract begins with a careful microscopic examination of the urine. A clean, voided specimen of a boy will usually suffice for this purpose but a catheterized specimen is preferable in girls in order to avoid contamination from the external genitals. The urinary sediment should be fresh when examined. Microscopic study for cellular elements, i.e., white blood cells, red blood cells, and casts, as well as stains, either methylene blue or Gram, for bacteria, should be done because it may detect the presence of infection and give some indication of the nature of the infection as much as forty-eight hours before a culture report of the urine can be obtained. Pus and blood in the urine without demonstrable bacteria may cause suspicion of a tuberculous process and influence one to do acid-fast stains or guinea pig inoculations. An amierobic pyuria, if a constant finding and substantiated by sterile cultures, may likewise suggest an entirely different type of chemotherapeutic approach.

Cultures of urines further define the nature of the infecting organism by identification, and this in turn permits a more selective form of chemotherapy. In isolated cases, further selectivity in drug therapy can be gained by the use of sensitivity tests, by determining effective concentrations for various drugs against the organism present.

Daily stains and/or cultures and frequent sensitivity tests may be essential in severe infections and their fluctuations from day to day may be of considerable importance in the management of the child's infection.

Further steps in the study of these children should proceed in a systematic, orderly fashion in order to minimize errors and omissions. This does not mean, of course, that one should pursue a routine course in a blind, unreasoning manner at the expense or sacrifice of sound clinical judgment. But it does implement such judgment and expedite the arrival at an accurate diagnosis if one follows a logical sequence of testing.

The presence or absence of residual urine must be determined early in these cases. The initial determination is the important one and great care should be taken to see to it that this is done accurately. Gentleness and a strict regard for asepsis should be exercised at all times. There is little risk if this is done. Prior instrumentation of any sort is likely to obscure the result, either by causing a retention by trauma where one did not exist before, or by aggravating a pre-existing one so that the accuracy of the observation is destroyed.

The type of catheter used will vary with the individual preferences of the physician. Our inclination is to use a small metal female catheter in girls, ranging from 10 Fr. to 16 Fr. according to age and size of the child, and an equally small semistiff condé catheter in boys. These are usually more certain of introduction, even by one inexperienced in their use, and offer less chance of becoming contaminated during insertion than a soft rubber catheter. The important thing is to insert a catheter promptly after a voiding to get a true measurement of the amount of residual and to get the catheter into the bladder with a minimum of trauma.

Cystography.—Cystograms furnish a permanent record of bladder contour and capacity. The amount of fluid introduced into the bladder for this purpose will vary with the size and age of the child. Males normally have a smaller bladder capacity than females.

The picture of the bladder which is obtained with some intravenous urograms may eliminate the need for cystograms in some cases because the latter frequently outline bladder diverticula, distortions of the bladder, or foreign bodies quite well as the contrast media accumulates in the bladder. They do not, however, disclose regurgitation into the ureters in the dramatic way that a cystogram does. For this reason alone, cystograms are quite useful and can easily be made a part of the examination for residual urine if one is prepared to do the cystogram before the catheter is withdrawn.

The amount of fluid opaque media put into the bladder for a cystogram depends upon the patient's bladder capacity. The fluid should be allowed to flow into the bladder by gravity without undue pressure. If a residual is

present and the amount known, the same or nearly as much fluid may be introduced into the bladder. If no residual is present, an amount of opaque fluid comparable to that expelled in an average voiding can be used for the cystogram. A nonirritating fluid such as sodium bromide ($7\frac{1}{2}$ per cent solution) makes an acceptable medium for cystograms.



Fig. 1.—Cystogram. F. D., age 9; 600 c.c. residual urine; bilateral regurgitation of ureters with hydronephrosis and hydroureter.

Intravenous Urography.—There is much less hesitancy now in employing this useful agent for diagnostic purposes than formerly. Few ill effects have been noted from its use although ordinary precautions should be observed if the child is very ill. Furthermore, excretion of the drugs used for this purpose is usually poor in the face of severe renal insufficiency.

Too much should not be expected of intravenous urography in all cases. Where renal function is good and no obstruction or stagnation is present, the media may be excreted so rapidly that little notion of kidney architecture is obtained. The best that can be said in these cases is that kidney function is present. On other films, the radio-opaque material will be of insufficient concentration to show well, or perhaps be so obscured by intestinal gas as to have little if any pictorial value. Better films may be obtained on the first plate made and the films are of no value unless taken very shortly (within two or three minutes) after the agent is injected. The most serious disadvantage to intravenous urography is that the films frequently fail to show minor defects in the kidney, defects which may be shown in very good detail in retrograde

studies. Many intravenous urograms simply cannot be interpreted and provide nothing more than some idea of the degree of impairment in renal function.

They do provide a more physiologic and anatomic record than retrograde studies in some instances, particularly where stasis is present and where function, even if somewhat impaired, is still present to some degree. They are of great value if for any reason cystoscopy and retrograde pyelograms are not possible. On rare occasions, intravenous studies may serve to tell the story when retrograde studies have been unsatisfactory.



Fig 2—Intravenous urograms D. W., age 13, kidney pelvises well outlined and most of ureters visualized, kidney outlines distinct.

Retrograde Pyelography.—The improvements made in infant cystoscopes in recent years have greatly facilitated the urologic investigation of children. Vision has been improved even as the instruments have been made smaller and we can now view the bladder and urethra in very young infants. Nevertheless, it should be kept in mind that the structures in the genitourinary tract of a child are not as large as those of an adult. This fact, coupled with the miniature size of the cystoscopes, somewhat restricts the accuracy of the urologist's report and further limits his ability to do some things cystoscopically for children which are everyday practice in adults.

The superiority of cystoscopy and retrograde pyelograms over intravenous urography lies in the obvious advantage of (1) actually seeing within the bladder and urethra, (2) being able to catheterize the ureters to obtain separate urines from the two kidneys for microscopic study and culture, (3) securing

differential quantitative functional tests of the two sides, and (4) making repeated retrograde pyelograms, if necessary, until satisfactory films have been obtained.

All urographic studies of the kidneys, ureters, and bladder are better if intestinal gas is minimal. Children, particularly infants, show a great deal of this, perhaps because of their habit of swallowing air. We have discarded the routine use of enemas and usually rely on sedation alone for precystoscopic preparation. If fluoroscopy or a scout film before radiographic studies reveals too much gas for satisfactory films, the intravenous urography or cystoscopy with retrograde pyelograms may better be postponed until another time. Intestinal gas does not interfere so much with retrograde pyelograms as a rule because of the greater density of the radio-opaque media possible in the latter.

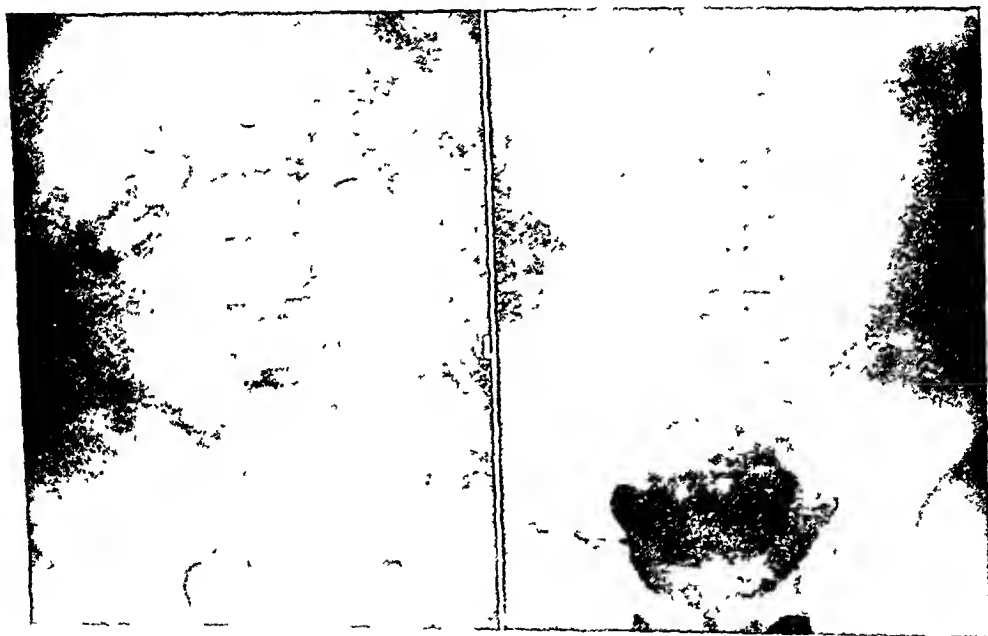


Fig 3.

Fig 4.

Fig 3.—Retrograde pyeloureterograms E. C., age 10; transurethral resection for bladder neck obstruction eight years previously.

Fig 4.—Intravenous urograms. Unsatisfactory urograms on same patient as in Fig. 3.

Exploration and Biopsy.—There always remain certain individuals in whom these diagnostic procedures and the exercise of the best clinical judgment still leave the diagnosis in doubt. Frequently one has to fall back upon surgical exploration of a doubtful mass in the flank or upon inspection and biopsy of a questionable lesion.

SURGICAL PRINCIPLES AND METHODS FOR DIFFERENT INFECTIOUS CONDITIONS

The fundamental principle in the management of all surgical complications of infections in the genitourinary tract is the prompt establishment of free drainage and the elimination of all stasis. Every effort must be made to pre-

serve tissues and structures and to restore them to normal function. Plastic or restorative surgery, therefore, plays an important role in the management of these cases.

Bladder Neck Obstruction.—Bladder neck and posterior urethral obstructions generally fall into two categories; those in which the basic factor of obstruction is *neurogenic* in origin and those in which a *mechanical* defect causes the obstruction. The former seemingly are less frequent in children than in adults. Examples of the neurogenic group include children who have spina bifida occulta, meningoceles, cord tumors, or injuries to the spine resulting in paralyses of the lower extremities and loss of vesical and anal control.

A conservative program of therapy is usually employed in these cases with particular emphasis on the control of infection. Some of these children will develop either an automatic bladder or a semiautomatic type of bladder after a period of time with a minimal amount of urinary disability.

The types of obstruction most common in children have recently been listed by Campbell¹ as follows: contracture of the vesical outlet, congenital valvular obstruction of the prostatic urethra, congenital hypertrophy of the verumontanum (colliculus seminalis), ureterocele, prostatic lobes, and neuromuscular disease.

We find it difficult sometimes to distinguish between the first two, while the verumontanum seems proportionately large in relation to surrounding structures in most small boys and therefore difficult to label obstructive in all instances. We have seen a few cases of prostatic enlargement in children as well as ureteroceles large enough to obstruct the bladder outlet. The neuromuscular vesical disease group represents those which have been listed above as neurogenic in origin.

In both types of obstruction, the same serious complications, stasis and infection, are present, with renal insufficiency as the eventual outcome if these two factors are not combatted successfully. The mechanical obstructions are more amenable to surgical correction and therefore offer a better prognosis unless too far advanced.

Transurethral resection of bladder neck obstruction can be accomplished successfully using miniature instruments. The limitations imposed upon the procedure by the small size of the involved structures and by the small size of the instruments should again be noted. In our opinion it is wiser to proceed cautiously and with extreme consideration for these tiny structures at the risk of having to repeat the operation one or more times rather than to risk an operative failure by overzealousness at the beginning. We are more and more inclined to keep the bladder intact while this is being done, provided a satisfactory method of insuring adequate renal drainage can be maintained during this period. Retention catheters in the bladder do not always provide this assurance, particularly in very young children. They certainly do not provide adequate renal and ureteral drainage in some cases of hydronephrosis.

Cystostomy does provide adequate drainage in most instances and may be advisable if diverticula of the bladder requiring removal are present. On the other hand, scalpel removal of bladder neck obstructions via a cystostomy is

notoriously inaccurate and difficult. Cystostomy has the added disadvantage of delaying one's evaluation of the outcome of the bladder neck surgery until the bladder has again become a closed viscus. Furthermore, it has not been proved that an open, and therefore contracted bladder, may not in fact contribute additional obstruction of the ureters by the pressure of the thickened bladder wall upon the intramural portion of the ureter.

Hydronephrosis and Hydroureter.—Dilated ureters arise from a variety of causes. Unexplained dilatations of a severe degree are sometimes catalogued as megaloureter or congenital hydroureter. These are usually infected and as a rule the kidney and ureter are so badly damaged as to necessitate nephroureterectomy if the condition is unilateral.

Dilatation of the ureter due to mechanical causes falls into two general classifications, those due to extrinsic factors and those of intrinsic origin.

The former consist primarily of aberrant vessels and of fibrous or scar tissue bands, either of which may be encountered anywhere along the ureter, though more commonly found near the ureteropelvic junction. Either separately or in conjunction, they can produce sufficient pressure on the ureter from the outside to cause obstruction and dilatation above the point of obstruction with resultant stasis, infection, and renal damage.

Surgical removal of either offers an excellent prognosis if done before irrevocable damage to the structures above the point of obstruction has occurred. Otherwise, nephrectomy has to be done. In many instances the condition is associated with a constriction of the ureter at the point of obstruction so that we have an intrinsic factor of obstruction to contend with as well as an extrinsic factor.

Intrinsic obstruction implies a disturbance within the ureteral wall or lumen itself, such as stricture, constriction, stenosis, a foreign body such as stone, or, on occasion, a ureteral tumor.

It is in stricture or stenosis of the ureter that one has an opportunity to exercise all his ingenuity to relieve the obstruction yet preserve the continuity of the ureter. A wide variety of techniques for this purpose have been described. The chief handicap to a successful operation is the fact that many of these ureters have been stretched to almost tissue paper thinness which makes any form of plastic repair difficult and the prognosis unfavorable.

Regurgitation of the ureters is an interesting phenomenon both because of its frequency and because of the uncertainty regarding its origin. It is quite commonly observed in bladder neck obstructions and might be regarded purely as a back pressure manifestation except for the fact that it is frequently unilateral and furthermore is seen at times where no bladder neck obstruction is present. A patulous orifice also might suggest a purely mechanical origin for regurgitant ureters, yet regurgitation can occur with orifices that are not patulous and appear quite normal.

The fact remains that many dilated and regurgitant ureters regain their normal tone and lose their dilatation if a bladder neck obstruction is successfully relieved. There does seem to be some relationship between the response

of the bladder wall and the response of the dilated ureter to an operation on the bladder neck, with both structures responding to about the same degree as a rule.

Anomalies of the Kidney.—The ordinary anomalies of the kidneys consist of single or polycystic disease, horseshoe kidneys, and ectopic kidney.

All of these conditions may be associated with infection and as a matter of fact pyuria is the presenting sign leading to their discovery in most instances.

The decision for or against surgical intervention in these cases, either in the presence or absence of infection, will depend upon one thing; namely, will surgery be helpful. Each case has to be handled individually.



FIG. 5.—Plain plate of urinary tract with ureteral catheters in place. J. M., age 12, bilateral renal calculi.

Tuberculous and Calculous Disease of the Kidney.—It is not the intent of this paper to discuss either of these two conditions except in so far as infection is concerned and the part that surgery may play in the management of that infection.

We have seen very little renal tuberculosis in children without evident tuberculosis elsewhere. Should a proved unilateral renal tuberculosis be encountered, nephrectomy would have to be given serious consideration, as is the case in adult renal tuberculosis. It may be, however, that further experience with streptomycin in tuberculosis will warrant a nonsurgical approach in the future.

Calculous disease in children is more often a medical or metabolic problem than a surgical one, usually with an infectious background which further complicates and aggravates the picture. Both kidneys are usually involved

and whether the kidney substance itself is riddled with calcium material or the pelvis and calyces are full of stones, surgery is likely to be impracticable and of no avail. Infrequently a stone fragment may break away from the parent mass and become lodged in the ureter, necessitating surgical removal. For the most part these children need every bit of living kidney substance which they have so that, rather than risk further mutilation of the kidney by surgery, one's efforts are confined to the control of infection by chemotherapy and the correction of metabolic errors in so far as possible.

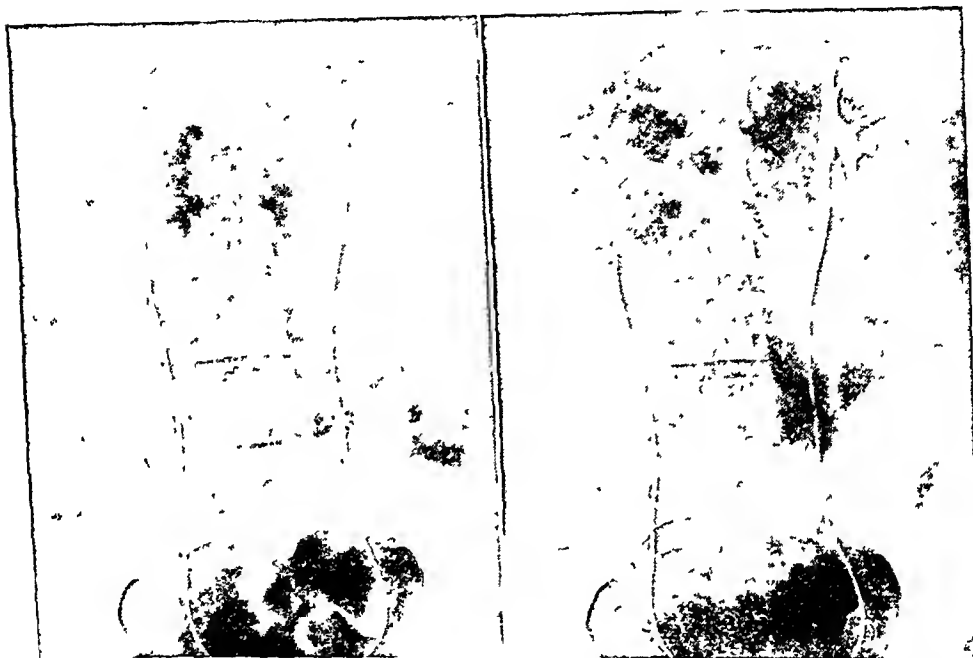


FIG. 6.

FIG. 7.

Fig. 6.—Plain plate of urinary tract with ureteral catheter in place. R. B., age 13; bilateral nephrocalcinosis.

Fig. 7.—Retrograde pyelograms. Bilateral pyelograms on same patient as in Fig. 6.

Factors Influencing the Type of Surgery Employed.—No simple criteria are available which will serve to make this decision an easy one. The urologist is confronted constantly with the choice of sacrificing a kidney or the perhaps more difficult task of trying to repair it. The genitourinary structures of a child always exhibit amazing inherent reparative properties and this may be the determining factor in choosing a more conservative course in individual problems.

There must be reasonable assurance before a nephrectomy is done that the remaining kidney will support life. There must also be the same assurance that if a reconstructive or plastic procedure is done on the involved kidney, it will be able to resume its normal function after operation, free of stasis and free of infection.

We have had a few instances of unilateral kidney disease, with or without infection but with hypertension, where the latter was the determining factor in nephrectomy. It should be emphasized, however, that a kidney is not removed solely for hypertension. There must exist findings indicative or suspicious of unilateral involvement so that one would feel that removal of the kidney would constitute no loss to the patient but instead a probable gain.

On occasion a heminephrectomy or calycectomy can be done to remove a diseased portion of a kidney, retaining the nondiseased portion. This is particularly true where a stone is embedded in a calyx and the calyx both dilated and infected. Removal of the stone alone would leave behind an area of stasis and infection which would predispose to the formation of other stones.



Fig. 8—Retrograde pyelograms. E. T., age 15. Unilateral hydronephrosis and hydroureter, left. hypertension, nephrectomy.

Gibson² in 1945 reviewed in detail the various technical procedures used in the repair of ureteral strictures and dilated kidney pelves. One of the most popular techniques is one in which an incision made downward along the course of the ureter through the strictured area is sutured across the course of the ureter at right angles to the incision. This is particularly adaptable to the stricture at the ureteropelvic junction associated with hydronephrosis.

As a rule no definite plastic procedure can be planned until the kidney or ureter has been exposed and the exact nature of the obstruction determined. Then, if a plastic repair is elected, one may either use a technique previously



Fig 9—Retrograde pyelograms. W. F., age three; bilateral hydronephrosis with tortuous redundant hydroureters.



Fig 10



Fig. 11.

Fig 10—Resection of redundant portion of right ureter with T-tube drainage and splint of ureter (same patient as in Fig. 9).

Fig 11—Same patient as in Figs 9 and 10 after left ureter had also been partially resected and T-tube inserted.

known or he may improvise one to cover the situation which he has encountered. Two things must be kept in mind: to construct something that will be free of stasis when it has healed and to provide adequate drainage of the parts during the convalescent period.

A nephrostomy may have to suffice on occasion where it is imperative to get quick drainage of an infected kidney with the minimum of surgical shock. However, permanent or semipermanent nephrostomies have one disadvantage. The usual nephrostomy drainage tube is difficult to maintain in place and to keep functioning.

A dilated ureter is a good site for drainage in hydroureter and hydronephrosis and we are finding the conventional T-tube a very satisfactory drainage tube in this location. It remains in place well and its drainage properties, which are good to begin with, can be greatly increased by making additional perforations in the tube.

We are finding, as others have, that it is possible to resect considerable portions of long, dilated, tortuous ureters as a part of a reconstructive procedure. It is obvious sometimes that, regardless of what produced the hydroureter originally, the condition has reached a point where the ureter and its contents become of themselves an obstructive factor that must be dealt with. Removal of redundant sections of such ureters, end-to-end anastomosis of the severed ends of the ureter as in intestinal surgery, and drainage of the ureter at some point beyond the point of anastomosis with a T-tube, helps straighten out the ureter and at the same time provides excellent drainage during the convalescent period. We have removed as much as four inches of ureter in at least one case, and we have left T-tubes in place as much as five and one-half months after their insertion; their removal after this period entailed nothing more than simply pulling them out. The sinus tracts healed promptly.

Diversion of the urinary stream by means of a ureterointestinal anastomosis or ureterocutaneous transplant, with or without cystectomy, is undertaken in children much as in adults. The indications for this in children are found for the most part in congenital anomalies of the bladder, such as extrophy.

COMBINED USE OF CHEMOTHERAPY AND SURGERY

The drugs most commonly used at the present time as urinary antiseptics are the various sulfonamide derivatives, penicillin, streptomycin, mandelic acid, methenamine, and the various alkalinizing agents.

Most of these children who have an infection in the urinary tract associated with or secondary to some surgical anomaly are quite ill. They need every assistance that can be given. Certainly every effort should be made to combat the toxicity of their infection as well as to prevent the spread of infection to the other genitourinary structures.

The preoperative use of chemotherapy, therefore, is advisable in most instances and should be continued during the postoperative period as long as fever or pyuria persist. Care should be taken in the selection of the drug or drugs employed, but once a selection has been made, full dosages should be

used. A great many children have received inadequate chemotherapy before they come to urologic study and have developed a tolerance to the drug which militates against its effectiveness at the time when the greatest need for its effectiveness exists, namely, just before and after operation.

Too much should not be expected of any antibacterial agent, however, so long as a mechanical problem involving stagnation or stasis remains unsolved. The most potent aid which can be given drug therapy is the restoration of a normal current of urine through the urinary passages. In other words, if surgery was indicated and has been done successfully, one expects more of chemotherapy after surgery than before.

The author wishes to express his appreciation to Dr. A. F. Hartmann and Dr. D. K. Rose for their generous assistance in the preparation of this paper.

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Clinical Conference

CONFERENCE AT RAYMOND BLANK MEMORIAL HOSPITAL FOR CHILDREN, DES MOINES, IOWA

LEE FORREST HILL, M.D., CHIEF OF PEDIATRIC STAFF

DR. HILL.—This morning we have five cases to show you. The first three deal with problems of premature infants. Dr. Spevak, will you tell us about the first patient?

Case 1. Retrolental Fibroplasia

DR. JACK SPEVAK (Resident in Pediatrics).—This premature female infant weighed 2 pounds, 14 ounces at birth. During the pregnancy the maternal diet was adequate and the mother had no illnesses. Except for some minimal vaginal bleeding during the early stages of labor, there were no undue complications. At birth the infant was moderately asphyxiated, but color and respirations returned to normal shortly after she was placed in the incubator. There are two siblings who are perfectly normal.

The infant's course in the nursery was uncomplicated. A formula using powdered half-skim milk was used, and during the first week ascorbic acid, 50 mg., and vitamin D, 600 units daily, were begun. Lighting in the nursery is available from south windows and ordinary ceiling lights are protected by frosted globes. An ultraviolet air sterilization lamp is positioned over the entrance to the nursery but direct rays from this light source are screened from the infants. At no time during the baby's twenty-seven days of hospitalization were any ocular abnormalities noted. However, no ophthalmoscopic examination was done.

At the age of 5 months the infant was brought to the hospital because the mother suspected the baby could not see. The baby weighed 11 pounds, 5½ ounces, and was 21 inches in height. On examination of the eyes, the first finding was the characteristic searching movements of a blind child. The eyeballs appeared to be smaller than normal. No red reflex could be seen but an intense bilateral opacity was clearly visible with an ordinary flashlight. This opacity was thought to be lenticular, and a diagnosis of bilateral congenital cataracts was agreed upon. Later the infant was seen in consultation by the ophthalmologist at the State University Hospital at Iowa City, Iowa, who reported a diagnosis of retrolental fibroplasia.

DR. CHARLOTTE FISK (Staff Pediatrician).—Another premature infant born two or three days previous to this infant and weighing approximately 1,200 Gm. developed the same condition, but only in one eye. The baby's mother was diabetic.

DR. CHARLES L. BURR (Resident in Pediatrics).—This case is an example of one of the newer problems of the premature infant. It is an ocular maldevelop-

ment consisting of a persistence of hyaloid artery branches and the tunica vasculosa lentis. Later, it is believed, there occurs an overgrowth of embryonic connective tissue in the vitreous to cause blindness, usually bilateral. Clifford and Weller¹ report that 23 per cent of premature infants weighing 2 to 3 pounds at birth later developed retrolental fibroplasia. Many postulates have been advanced to attempt an etiologic explanation but as yet there is no proof for any. The two most popular at present are (1) precocious exposure of the premature infant to light, and (2) fetal anoxia. Warkany's experiments² with vitamin A deficiencies in rats suggest a relationship between retrolental fibroplasia and the maternal lack of vitamin A. However, Stewart Clifford reports the disease developing in premature infants who received 5,000 U.S.P. units of water-soluble vitamin A daily. In addition, one premature infant developed the disease who received the oral vitamin as mentioned and also a daily intramuscular injection of 20,000 U.S.P. units of vitamin A in oil.

The parents may be the first to notice that the infant does not see, for the manifestations first appear between 4 and 6 months of age. The searching nystagmus is often the outstanding characteristic first noticed. Further inspection may reveal one or several other characteristics of the disease; e.g., microphthalmia, shallow or absent anterior chambers, fetal-blue color of the irises, and an opacity occurring *behind* the lens. This latter point is stressed because we stubbed our toes at the first examination of the ocular opacities. Originally we had diagnosed bilateral congenital cataracts and were chagrined at not recognizing the condition earlier. However, a second choice diagnosis of retrolental fibroplasia was confirmed by the ophthalmologist.

In the sporadic unilateral cases occurring in the full-term infants, an erroneous diagnosis of retinoblastoma accounted for needless enucleations. Several types of treatment have to the present time been unsuccessful. Parents should be warned of the 5 per cent chance of glaucoma developing in this disease, as effective therapy for this complication is available.

Follow-up Note

This infant is now 9 months of age. Allowing two months for prematurity, the baby is still markedly retarded in its neuromuscular development. The head measures only 16.5 inches in circumference as compared with a chest circumference of 18.5 inches. In this case, then, the eye defect is associated with a cerebral defect.

Case 2. Anemia in a Premature Infant

DR. BRACK I. KNAPP (Resident in Pediatrics).—This 8-month-old white female infant was admitted to the hospital with the chief complaints of pallor and failure to gain weight for three months prior to admission.

The infant was delivered six weeks prematurely and was the second of a pair of twins, her twin sister being stillborn. Birth weight was 4 pounds, 6 ounces. The mother was anemic throughout her pregnancy, and was given liver extract weekly by injection and iron by mouth daily. Family history revealed a paternal aunt with severe anemia who had five miscarriages before the birth of a living child.

The infant was breast-fed for one month before being placed on an evaporated milk formula. She appeared to gain weight normally, weighing 13 pounds at 5 months of age. The mother noticed the infant's pallor soon after birth but was unconcerned because of the apparently normal physical and mental development. Since the age of 5 months she had become increasingly listless and apathetic, sleeping most of the time, showing little activity, and taking no interest in her surroundings. She had consistently refused both solid food and orange juice, although vitamin supplements had been maintained. Her weight on admission was the same as her weight three months previously, 13 pounds. Two severe upper respiratory infections occurred at 3 months and at 7 months of age. She was placed on iron three and one-half weeks prior to admission but no improvement had been noticed by the mother up to the time of admission.

Physical examination was essentially negative except for the marked pallor and listlessness. Neither the liver nor spleen was palpable. No petechiae were observed. Rectal temperature was 100° F.

Examination of the blood disclosed a red blood cell count of 2,580,000 with 4.3 Gm. of hemoglobin and a leucocyte count of 6,900 with 3 eosinophiles, 5 stab cells, 17 segmented cells, and 75 lymphocytes; there were 3 nucleated red blood cells per 100 white cells counted. Color index was 0.55. An hematocrit unfortunately was not obtained until after the first blood transfusion, which would make any volume index or mean corpuscular hemoglobin concentration calculated from such a value entirely inaccurate. For what it is worth, the value was 30 per cent. The blood smear showed pronounced anisocytosis with poikilocytosis with many hypochromic macrocytes and microcytes. There was considerable polychromasia and rarely a nucleated red cell was observed. The platelet count was 180,000; bleeding time, 1 minute, 45 seconds, clotting time, 6 minutes; clot retraction began in 45 minutes and was complete in 3.5 hours.

The day after admission a transfusion of 140 c.c. of whole blood was administered and at the time of presentation to this clinic the baby's appearance had already improved markedly.

DR. HILL.—This case is presented as an example of the problem with which one is confronted when a case of anemia in infancy presents itself for diagnosis. Since the report of Zuelzer and Ogden³ on macrocytic and megaloblastic anemia was published, we have been on the alert not to overlook this possibility. While this case may well be one of iron deficiency anemia, nevertheless, other causes for the anemia should be carefully scrutinized. Dr. Knapp will discuss some of the differential points to be considered in some of the more common anemias of infancy.

DR. KNAPP.—In discussing the various types of anemias which may occur during infancy, it seems important in the diagnosis of this case to mention Diamond's classification briefly:

1. The normocytic normochromic anemias—including aplastic anemia, chronic hypoplastic anemia, and the anemia of prematurity.

2. The macrocytic hyperchromic anemias—pernicious anemia of childhood and the megaloblastic anemia of Zuelzer.

3. The microcytic hypochromic anemias—including iron deficiency anemia and the anemia of congestive splenomegaly.

4. The anemias associated with jaundice—hemolytic anemias, such as Cooley's anemia, congenital anemia, sickle cell anemia, and erythroblastosis fetalis.

In consideration of this infant's anemia the factor of prematurity is certainly present, but the anemia of prematurity usually develops during the second month after birth, reaching its greatest severity by the end of the third month. This infant's anemia, while probably present in the second and third months, did not influence her behavior and weight gain until 5 months of age. Diamond states that infants from mothers who themselves develop anemia late in pregnancy develop a profound anemia somewhat later, from the third to the ninth month. Hypochromic erythrocytes with a tendency toward microcytosis may be evident in the peripheral blood in the later stages but the hemoglobin rarely falls below 7.5 Gm. per 100 c.c. This infant's hemoglobin was 4.3 Gm.

Another type of anemia usually included in the normocytic normochromic anemias is that due to infection. A mixed type of anemia with both macrocytes and microcytes may be present, and once the foci of infection have been removed the anemia rapidly improves. This case, with a past history of infection, could easily fall in that category.

The macrocytic hyperchromic anemias are rare in childhood, but Blackfan and Diamond reported a series of fifteen patients between the ages of 4 and 16 months with anemias corrected by the parenteral administration of liver extract. Zuelzer⁴ states the following criteria should be present before a diagnosis of megaloblastic anemia can be made:

1. The presence of a severe normochromic anemia, usually but not invariably macrocytic, with a wide spread in the corpuscular diameters. (This picture was certainly true in our infant. The hemoglobin in one of Zuelzer's cases was 5.7 Gm. This infant had a hemoglobin of 4.3 Gm.)

2. A tendency toward leucopenia and neutropenia with the presence of giant metamyelocytes and hypersegmented neutrophils in the peripheral blood. (Neutropenia was moderately present in our patient but no metamyelocytes were noticed, although a few normoblasts were found.)

3. A diminution of platelets often associated with purpura or petechiae. (Platelets were only moderately reduced in our patient, appearing "numerous" on direct examination of the blood smear. No symptoms of capillary fragility were noted.)

4. An atypical bone marrow pattern, consisting of marked numbers of megaloblasts, although in the early stages there may be a pattern intermediate between normoblastic and megaloblastic erythropoiesis. (No marrow studies have been done at the time of this conference.)

Clinically, in megaloblastic anemia evidence of infection is usually present; the nutritional history is usually poor; weakness, pallor, loss of appetite, and irritability are present; splenomegaly is rarely found although the liver is usually increased in size. All of these symptoms are present in this infant and we will have to consider megaloblastic anemia very strongly in our differential diagnosis.

Since no jaundice was present in this case and no familial history of hemolytic anemia was given, the group of hemolytic anemias can be fairly well excluded. There is left, then, the anemia due to iron deficiency. The characteristic blood picture is one of a microcytic hypochromic anemia with the red blood count about 4,000,000 and the hemoglobin less than 10 Gm., usually between 4 and 8 Gm. A relative lymphocytosis is present (Not in our case!) but platelets are normal in number and no bleeding tendency is observed. The blood smear may show poikilocytosis, anisocytosis, and polychromasia, just as was reported in this case. The color index ranges from 0.40 to 0.80. (In this case it was 0.55.)

In conclusion, it would appear that the case presented fits either the picture of a megaloblastic anemia or an iron deficiency anemia, both of which are essentially "nutritional" anemias, and the presence of megaloblasts in the bone marrow would be the determining differential point.

DR. HILL.—Dr. Amick was in Buffalo at the area meeting of the American Academy of Pediatrics and heard Dr. Zuelzer give a paper on megaloblastic anemia in childhood. Dr. Amick, will you comment on this case?

DR. PERRY AMICK (Staff Pediatrician).—Dr. Zuelzer said the finding of only a few very large cells in the peripheral blood in a case of anemia is strongly suggestive of megaloblastic anemia. This can be proved by examination of the bone marrow, which shows many large megaloblasts.

Follow-up Note

Bone marrow studies were done the same day the case was presented in clinic and the following is the pathologic report: "The particles of marrow from the left tibia are very cellular and show an apparent predominance of erythropoietic tissue. This tissue contains a few megakaryocytes. Eosinophiles are fairly numerous. Smears demonstrate a relative increase in normoblasts, while megaloblasts are not encountered. The granulocytes are not remarkable. In summary, there seems to be normoblastic hyperplasia of the bone marrow, secondary to hypochromic anemia."

The above report is fairly conclusive evidence that the infant's anemia was one due to iron deficiency and was not a megaloblastic anemia.

Iron in the form of ferrous sulfate was prescribed in a dosage of 7.5 grains daily. A blood count one month later was as follows: Red blood cells, 4,420,000; white blood cells, 14,000; hemoglobin, 12 Gm.; differential, 3 eosinophiles, 49 segmented cells, 44 lymphocytes, and 4 monocytes.

Case 3. Premature Infant Weighing Less Than 1,000 Grams

DR. J. B. SCHUNK (Assistant Resident).—The patient was a severely asphyxiated female newborn infant, delivered by a double footling presentation at 4:43 A.M. on May 8, 1948. The mother, a gravida vi, para ii, had been admitted to the obstetrical service three days previously with vaginal bleeding. The diagnosis of pregnancy was apparently in doubt. A Friedman test was attempted but the animal died. No fetal heart tones were heard. There was a history of three spontaneous abortions, all in the first and second trimesters with cause undetermined. Gestation had apparently been uneventful. Date of last

menstrual period was "sometime in September, 1947." Diet had been adequate with vitamin and mineral supplement.

She was discharged in twenty-eight hours and upon readmission both feet and lower legs of the baby were protruding from the vagina and she was delivered in a few minutes. The infant surprised the physicians by crying soon after delivery and was placed in the premature nursery. The color was deeply cyanotic and respirations were gasping and irregular. Precursory physical examination was otherwise negative.

Continuous oxygen, 3 to 4 L. per minute, was delivered by a hood. The upper respiratory passages were suctioned with a catheter. An effort to maintain body heat was made with hot water bottles and automatic regulation of the room temperature at 85° F. Humidity was controlled at 50 per cent. One milligram of vitamin K was given hypodermically. The infant was not handled except when absolutely necessary.

At 8 P.M. on the day of birth, a dark red discharge from the rectum was noted. The vitamin K was repeated. The rectal bleeding, mixed with meconium, recurred in small amounts during the following forty-eight hours, then ceased. On May 9, about thirty-eight hours after birth, 15.0 c.c. of normal saline was given subcutaneously and 15.0 c.c. of 5 per cent dextrose in distilled water was given by gavage. These feedings were repeated at six-hour intervals until late in the third twenty-four-hour period following delivery, when the infant showed good swallowing ability and feedings with powdered half-skim milk were begun in the amount of 7.2 c.c. offered every three hours with a soft, rubber-tipped dropper. At the same time 3½ per cent amino acid mixture was administered subcutaneously, 15.0 c.c. every eight hours.

The weight was obtained on the third day and found to be 889 Gm. (1 pound, 14 ounces).

The total cubic centimeters per kilo of body weight per twenty-four hours during the second, third, and fourth days was 67, 131, and 115, respectively. The calorie intake per kilo of body weight per twenty-four hours rose from 6.7 calories on the second day to 106 calories on the fourth day.

Sixty thousand units of penicillin as procaine penicillin in oil were given daily to combat infection.

The baby showed surprising vigor and had a good cry after the first day of life. With the strong swallowing reflex and promising clinical course, a favorable prognosis was hopefully made. However, on the morning of May 12, the fifth day of life, she suddenly began having apneic periods with deep cyanosis. Physical examination was negative. There was no respiratory obstruction, the lungs were clear, and the trachea in the midline. Alpha-loheline, 0.5 c.c., was given hypodermically. Despite constant care and frequent use of artificial respiration, the infant expired at 8:20 P.M.

Consent for a post-mortem examination was given with the request that the head be excluded.

DR. HILL.—Dr. Davis, will you give us a report of the autopsy findings?

DR. S. K. DAVIS (Resident in Pathology).—This female infant presented few findings at autopsy that will aid much in the discussion. The weight was

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stimulants, and suction devices are valuable. Intermittent use of carbon dioxide-oxygen mixtures is sometimes recommended.

It would appear that the routine use of prophylaxis against infection is indicated in premature infants. Procaine penicillin in oil, administered in small daily doses, seems well suited for this purpose.

The tendency of the premature to develop acidosis has been repeatedly emphasized as one of the manifestations of inadequate renal function. Gordon has commented on the unreliable selective renal activity in utilization of sodium chloride solutions of the premature as compared with the full-term infant. The poor stores of vitamins with which the premature infant is equipped make early administration of supplements advisable. Especially is this true of vitamins C and K, which are given parenterally from the first day of life. Other vitamins are usually started on the fourth or fifth day.

There are other defects which the premature infant must combat: incomplete development of the enzyme system, hepatic immaturity, inadequate hematopoiesis, etc., all too much to discuss this morning. One phase of management, however, has been intentionally postponed to this point. The questions of when to inaugurate feeding, what food to use, and mode of administration, can be perplexing when suddenly foisted upon the physician. The feeding management of the very small premature infant has received little special attention in the literature. The infrequency of extremely small infants that give promise of survival does not seem to warrant a formal schedule, yet some sort of guide must be kept in mind. Overloading the infant with fluids and feeding mixtures in an effort to achieve early weight gain is perhaps the greatest hazard. The clinical appearance of the patient, of course, is the ultimate criterion, yet maintenance at an optimum is desired.

The first feeding should be after 48, possibly 72, hours of life. Feeding in the very small prematures should be by gavage and continued by that route until swallowing is possible without exhaustion after feeding. The total twenty-four hour intake must be carefully recorded and a gradual increase made to 160 c.c. per kilogram of body weight per twenty-four hours by the tenth to fourteenth day. The caloric intake can be increased at a slow rate also, reaching 125 calories per kilo in twenty-four hours at about the same time. Five per cent dextrose in distilled water may be offered in the first feedings with milk added in the second twenty-four hours of feeding. The proportion of milk to water may be gradually increased so that the feeding mixture is entirely milk by the tenth day. The addition of water to milk does not increase the digestibility of the milk, of course, but only tends to lessen the amount of milk taken. If smaller feedings are desired, the water portion of the feedings may be given subcutaneously as 2.5 per cent dextrose in water or $3\frac{1}{2}$ per cent amino acids mixture. For the past several years we have been using a powdered one-half skim milk preparation (Alaeta) as the food of choice for premature infants. This has been prepared as a mixture of 87 Gm. (10 tablespoons) of the powdered milk added to 600 c.c. (20 ounces) of water with 30 Gm. (1 ounce) of carbohydrate in the form of a dextrin and maltose preparation added. The percentages of total calories in protein, carbohydrate, and fat supplied by this food are, respec-

810 Gm. and the baby measured 34 cm. crown to heel. Skin and sclerae demonstrated a mild icterus. There were no other external abnormalities. There was a small amount of xanthoehronic peritoneal fluid. There were no abnormalities of the abdominal or pelvic contents in situ. The thoracic viscera were not remarkable aside from a rather marked venous engorgement of the large root veins and right atrium. The lungs were adequately inflated and showed no evidence of pneumonia. There were no abnormalities of the heart. The semifluid content of the jejunum and ileum was a foamy pinkish red. This was not present in other parts of the gut and no basis for the presence of blood could be ascertained. Examination of the brain was not permitted.

DR. HILL.—The survival rate of premature infants weighing less than 1,000 Gm. is about 10 per cent. Prematurity in itself is not an acceptable cause of death, except perhaps in the very small infants such as this one. In reviewing our management of this case we feel we may have been guilty of a common error—that of overdoing the fluid and food administration.

Approximately 50 per cent of the neonatal mortality rate occurs among prematurely born infants. Many of these lives could be saved with expert medical and nursing care. Providing the premature infant does not have a congenital defect inconsistent with life, escapes injury in the birth process, and avoids infection, his chances for survival should be good.

Dr. Schunk has prepared some remarks on the special hazards imposed by prematurity.

DR. SCHUNK.—During the sixteen-month period from January, 1947, through April, 1948, there have been 2,868 admissions to the newborn service of the Iowa Methodist Hospital. Of these, 210 or 7.3 per cent of the total were premature, weighing 2,500 Gm. (5½ pounds) or less. Of these, 36, or 17.1 per cent, have died, leaving a survival rate of 82.9 per cent.

The percentage of survivals of the various weight divisions of these premature infants was:

WEIGHT	ADMISSIONS	DEATHS	SURVIVAL (%)
2,001 to 2,500 Gm. (under 5 pounds, 8 ounces)	135	9	93.4
1,501 to 2,000 Gm. (under 4 pounds, 6 ounces)	41	7	82.9
1,001 to 1,500 Gm. (under 3 pounds, 5 ounces)	24	11	54.2
Less than 1,000 Gm. (under 2 pounds, 3 ounces)	10	9	10.0

These survivals compare favorably with anticipated percentages under good care that have been suggested by Dunham.

The handicaps of the premature infant's early existence are the inevitable result of the general immaturity of all the major systems. The proportionate increase in body surface and lack of subcutaneous tissue make maintenance of body heat difficult. The infant just discussed was kept in a premature nursery housing eight bassinets, with the obvious disadvantage of no ideal environment for any of the tenants. The frequency with which the premature infant displays irregular respirations and periods of apnea that may appear any time in the neonatal life reflects the inadequacy of the central nervous system. Convenient apparatus for the administration of oxygen, constant nursing care, respiratory

stimulants, and suction devices are valuable. Intermittent use of carbon dioxide-oxygen mixtures is sometimes recommended.

It would appear that the routine use of prophylaxis against infection is indicated in premature infants. Procaine penicillin in oil, administered in small daily doses, seems well suited for this purpose.

The tendency of the premature to develop acidosis has been repeatedly emphasized as one of the manifestations of inadequate renal function. Gordon has commented on the unreliable selective renal activity in utilization of sodium chloride solutions of the premature as compared with the full-term infant. The poor stores of vitamins with which the premature infant is equipped make early administration of supplements advisable. Especially is this true of vitamins C and K, which are given parenterally from the first day of life. Other vitamins are usually started on the fourth or fifth day.

There are other defects which the premature infant must combat: incomplete development of the enzyme system, hepatic immaturity, inadequate hematopoiesis, etc., all too much to discuss this morning. One phase of management, however, has been intentionally postponed to this point. The questions of when to inaugurate feeding, what food to use, and mode of administration, can be perplexing when suddenly foisted upon the physician. The feeding management of the very small premature infant has received little special attention in the literature. The infrequency of extremely small infants that give promise of survival does not seem to warrant a formal schedule, yet some sort of guide must be kept in mind. Overloading the infant with fluids and feeding mixtures in an effort to achieve early weight gain is perhaps the greatest hazard. The clinical appearance of the patient, of course, is the ultimate criterion, yet maintenance at an optimum is desired.

The first feeding should be after 48, possibly 72, hours of life. Feeding in the very small prematures should be by gavage and continued by that route until swallowing is possible without exhaustion after feeding. The total twenty-four hour intake must be carefully recorded and a gradual increase made to 160 c.c. per kilogram of body weight per twenty-four hours by the tenth to fourteenth day. The caloric intake can be increased at a slow rate also, reaching 125 calories per kilo in twenty-four hours at about the same time. Five per cent dextrose in distilled water may be offered in the first feedings with milk added in the second twenty-four hours of feeding. The proportion of milk to water may be gradually increased so that the feeding mixture is entirely milk by the tenth day. The addition of water to milk does not increase the digestibility of the milk, of course, but only tends to lessen the amount of milk taken. If smaller feedings are desired, the water portion of the feedings may be given subcutaneously as 2.5 per cent dextrose in water or $3\frac{1}{2}$ per cent amino acids mixture. For the past several years we have been using a powdered one-half skim milk preparation (Alacta) as the food of choice for premature infants. This has been prepared as a mixture of 87 Gm. (10 tablespoons) of the powdered milk added to 600 c.c. (20 ounces) of water with 30 Gm. (1 ounce) of carbohydrate in the form of a dextrin and maltose preparation added. The percentages of total calories in protein, carbohydrate, and fat supplied by this food are, respec-

tively, 23.5 per cent, 57 per cent, and 19.2 per cent. This approximates the caloric distribution of the foods recommended by Gordon and co-workers⁵ and by Powers.⁶ The caloric content is about 0.81 calorie per cubic centimeter of feeding (approximately 22 calories per ounce). Although no planned study has been made, the general impression of our experience with this food has been very satisfactory. The Hess schedule has been used in this hospital for a number of years and has proved to be a useful and reliable guide. The workers already referred to have demonstrated large groups of patients with controls over long periods of time that have shown greater weight gains on half-skim milk than on other isocaloric feeding selections, including breast milk. The many arguments presented for the reduction of fat and increase of protein in the premature feeding are convincing.

Case 4. Primary Tuberculosis

DR. M. E. ALBERTS (Intern in Pediatrics).—J. C., a white female infant aged one year, 11 months, entered the hospital with the complaint of red "bumps" on the legs. These had first appeared one week previously on the right leg and two to three days later on the left leg. The child was seen by a private physician three days previous to her admission here, at which time there were several discrete, firm, red, tender, nonpruritic, ovoid nodules in the skin over the anterior tibial aspect of both legs, and one such lesion on the right buttock. These nodules were about 1 to 1.5 cm. in diameter and their long axis tended to lie in the longitudinal plane of the legs. A tuberculin test was done by the Mantoux method, using 1/100 mg. old tuberculin. A 3+ positive reaction was obtained.

At the time of admission to the hospital the nodules on the right leg were beginning to soften and presented the bluish-yellow color characteristic of a simple contusion.

The history of the patient revealed contact with a man who has untreated tuberculosis. The child's parents manage a tavern and maintain their home in the rear of the same building. The child, therefore, comes into close contact with the patrons of the tavern, and has had especially close contact with the man in question. The parents of the child state that the same man is held responsible for another person becoming infected with tuberculosis . . . that person is now being treated in a local hospital. Careful inquiry uncovered no other possible source of tuberculous infection. Both parents are having chest x-rays made at the present time.

The past history of the child reveals nothing of significance. She has had occasional colds, had thrush three months ago, and during the first year of life had roseola infantum. Her birth weight was 7 pounds, 4 ounces; her present weight is 24 pounds, 4 ounces.

Physical examination is essentially negative with the exception of the nodules in the skin. The lungs are clear anteriorly and posteriorly to auscultation and percussion. However, x-ray of the chest reveals a patchy pneumonia extending from the right hilus to the diaphragm in the medial half of the right lung. The rest of the lung fields are clear (Fig. 1).

The laboratory findings are as follows: red blood cells, 4,230,000; hemoglobin 11.8 Gm.; white blood cells 14,750 with 68 per cent polymorphonuclear cells, 31 per cent lymphocytes, and 1 per cent monocytes. The blood sedimentation rate (Wintrobe) was 100 mm. in one hour. Gastric washings for acid-fast organisms have been negative on three occasions. Stool examination for acid-fast organisms has also been negative. A guinea pig has been inoculated with some of the concentrated gastric washings. Kline and Kahn tests are negative.

The patient's course in the hospital has been afebrile, although the temperature does show fluctuation of a nonspecific nature. She has been receiving streptomycin, 1.0 Gm. per day, in divided doses.

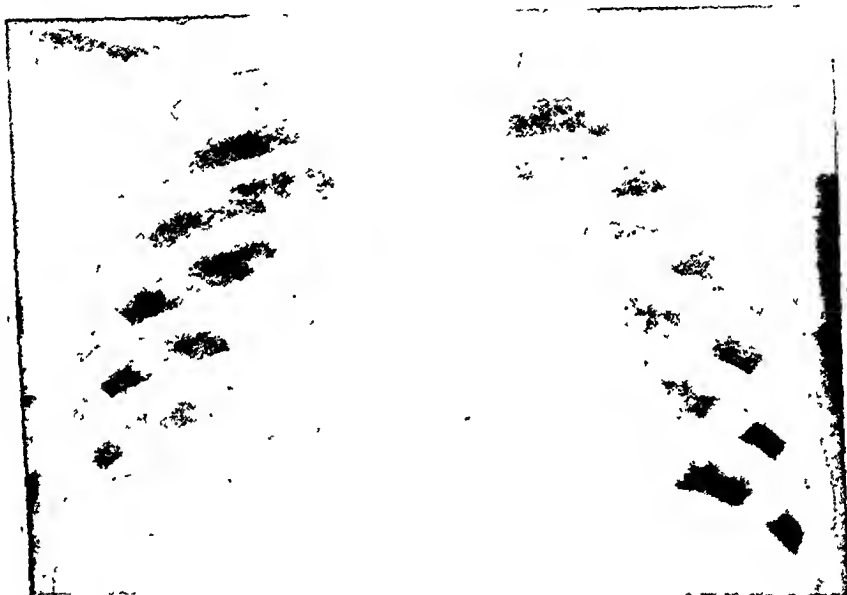


Fig. 1.—Film taken before streptomycin therapy shows pneumonic shadow in right hilus.

DR. HILL.—The lesions on the legs of this child were typical of erythema nodosum. The most common underlying causes of erythema nodosum in children are primary tuberculosis and rheumatic fever. However, rheumatic fever is unlikely because of the patient's age. Primary pulmonary tuberculosis, including both the parenchymal and lymph node components, can seldom be diagnosed by physical examination alone. As in this case, diagnosis rests upon the reaction to tuberculin and upon the x-ray. Even after we had seen the x-ray film and had gone back over the right lung meticulously, no abnormalities could be detected.

This is the first case of primary tuberculosis in the acute stage that we have seen in this hospital since streptomycin became available. Whether or not to use the drug for J. C. was debated at some length. In the great majority of children the lesions of primary tuberculosis retrogress over a period of months

and finally calcify or even disappear altogether. However, in the first four years of life, and especially in infancy, progression from the primary complex may occur and give rise to such fatal forms of tuberculosis as miliary tuberculosis, tuberculous bronchopneumonia, and tuberculous meningitis. In the event that any of these forms emerged in this patient, streptomycin would certainly be employed. It seemed reasonable, therefore, to consider the use of streptomycin from a preventive point of view (prevention of the fatal forms). For this purpose a relatively small dose, given over a shorter period of time, might suffice. Objections to streptomycin include the danger of damage to the eighth nerve and to the vestibular apparatus, and the less substantiated risk that a resistant organism might emerge which, if communicated to others, would give rise to tuberculous disease not susceptible to drug therapy. Since danger of spread in primary tuberculosis is minimal anyway, the latter objection did not seem too important.

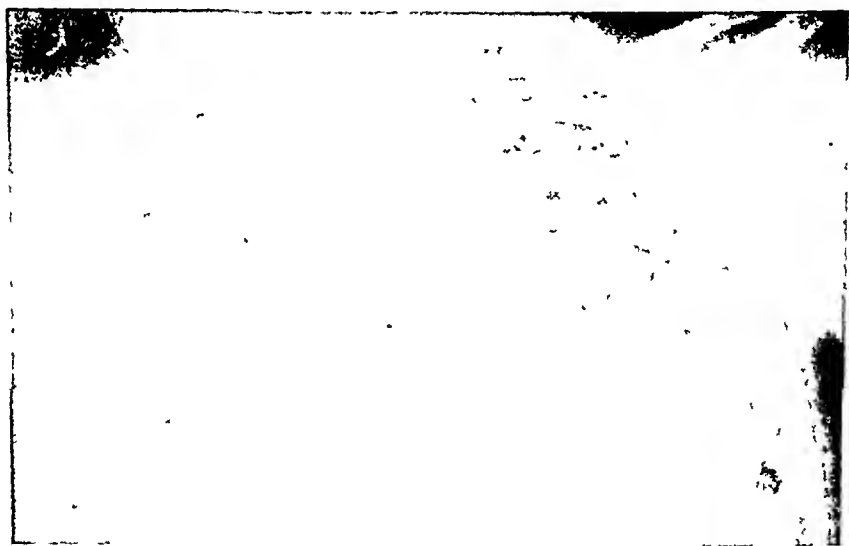


Fig 2—Film taken approximately one month after one week of streptomycin therapy. Shadow essentially unchanged.

We should have liked to have kept our patient on streptomycin for two weeks, but we had to be content with seven days. The sedimentation rate taken at the end of this period had dropped from the original 100 to 40 mm. in one hour. The nursing staff reported the child had become much more active and that her appetite had improved greatly. A repeat x-ray film of the chest, however, showed no essential change in the parenchymal lesion.

Another observation we had hoped to make was the effect of streptomycin on the tuberculin reaction. Presumably, if the drug could be given to the point of destruction of all tubercle bacilli, a positive reaction would change to a negative one. Obviously, the period of streptomycin administration in this case was too short to permit of any conclusions. However, a repeat test was done with

the same preparation of old tuberculin and with the same dosage ($\frac{1}{100}$ mg.). The resulting reaction, while positive, was approximately one-half the size of the original reaction.

Follow-up Note

The sedimentation rate one month later was still 41 mm. in one hour. The roentgenogram (Fig. 2) was essentially unchanged. A third tuberculin test with $\frac{1}{100}$ mg. old tuberculin gave a positive reaction approximately one-fourth the size of the original test. The child had gained 1.5 pounds in weight and was symptom free.

Case 5. Salicylate Intoxication

DR. R. J. BYRUM (Assistant Resident in Pediatrics).—This 9-year-old white boy, weighing 72 pounds, had a six-day history of migratory joint pain and joint swelling associated with a low-grade fever prior to admission. No history of recent respiratory infections or past rheumatic manifestations could be elicited. Examination revealed a febrile (102.4° F.), acutely ill boy whose pharynx was moderately inflamed. His left cardiac border seemed slightly enlarged to the left, and though no murmur could be heard there was an accentuated second sound over the aortic area. The right ankle and left knee were moderately swollen, warm, and extremely tender to palpation.

Laboratory data included an erythrocyte count of 3,520,000, hemoglobin 12.6 Gm., and a leucocyte count of 10,400 with a differential of two eosinophiles, 4 stab cells, 58 mature polymorphonuclears, and 36 lymphocytes. The sedimentation rate (Westergren method) was 111 mm. per hour. Urinalysis, Kahn and Kline, and Mantoux tests were negative. A roentgenogram of the chest was interpreted as revealing a normal heart size, but the cardiac configuration suggested a mitral valve lesion. The electrocardiogram showed a prolonged P-R interval.

After making a diagnosis of rheumatic fever, 60 grains of sodium salicylate daily were ordered. Due to an error, additional salicylates were given in the form of acetylsalicylic acid, grains 30 daily, to make a total of 90 grains of salicylate administered daily. The symptoms rapidly improved and the arthralgia had subsided by the fifth hospital day. On the evening of the sixth day the patient became confused and began to develop hyperpnea and restlessness. By the following morning he appeared slightly cyanotic, complained of a headache, was mentally confused, and respirations continued to be deep and pauseless. There was no fever. Slight nuchal rigidity and dryness of the mucous membranes were also noted. A carbon-dioxide combining power was 31 volumes per cent and a blood salicylate level of 40 mg. per 100 c.c. (400 gamma) was obtained.

Oxygen was immediately begun, all salicylates were discontinued, and intravenous fluids were ordered to hasten urinary excretion of the drug. One ampule of Synkamin and 100 mg. of ascorbic acid daily were also added as prophylactic treatment of a possible prothrombin disturbance. Two days later the salicylate level was 12 mg. per cent and the child was much improved. Hyperpnea was no longer present and he appeared bright and alert. Because of the still elevated

sedimentation rate of 115 mm. per hour, sodium salicylate (60 grains) was again instituted, but was decreased to 45 grains two days later when a salicylate level of 29 mg. per cent was obtained. Since that time the patient has been maintained on that dosage with no further toxic manifestations.

DR. JOE M. STANDEFER (Staff Pediatrician).—The relatively recent popularization of massive salicylate therapy in rheumatic fever has, no doubt, increased the number of salicylate intoxication cases. With this increase there has developed a finer understanding of the mechanisms involved in this dramatic symptom complex.

Salicylates have been used for many years to alleviate the symptoms of the common cold and rheumatic fever. It has long been known that infants under one year of age tolerated aspirin very poorly and it has recently been emphasized that younger children could not tolerate doses of salicylates thought to be safe for adults; namely, 0.13 to 0.19 Gm. per kilogram of body weight daily.⁷ It has recently been shown that aspirin produces toxicity more readily than sodium salicylate in young children.⁸

The signs of salicylate toxicity are: (1) hyperpnea, which is deep and pauseless and comparable with the hyperpnea of diabetic acidosis; (2) apathy and lassitude; (3) anorexia, which may be severe; (4) tinnitus; (5) dizziness; (6) irritability and restlessness; (7) disorientation, stupor, and convulsions; (8) thirst; (9) sweating; (10) fever, which may be high; (11) abdominal pain; (12) pallor and cyanosis; (13) epistaxis and hemorrhagic phenomena; and (14) dehydration.

The laboratory findings which confirm salicylate intoxication are: (1) increased prothrombin and coagulation times and an elevated blood chloride level; (2) urinary findings; e.g., (a) reduction of copper by salicylate compounds, (b) positive Gerhardt's test, (c) acetone and diacetic acid, and (d) albumin, casts, white and red blood cells indicating renal damage; (3) salicylate blood levels over 32 and commonly over 40 mg. per cent; (4) the pH of the blood is initially elevated; later the pH may be reduced with an associated acidosis; and (5) the carbon-dioxide combining power alone is unreliable in salicylate intoxication. It may be normal or depressed even with an elevated pII of the blood. However, if values for both the carbon-dioxide combining power and pII of the blood are available, they provide valuable information to guide in giving correct therapy.

MECHANISM OF SALICYLATE INTOXICATION

The mechanism responsible for the development of respiratory alkalosis in salicylate intoxication is hyperventilation. The hyperventilation or hyperpnea is deep and pauseless, and is probably due to a disturbance in the respiratory center. As the hyperventilation progresses there is a loss of carbon dioxide from the alveoli of the lungs which is followed by a loss of carbon dioxide from the blood. This causes a derangement of the H_2CO_3 : BHCO_3 ratio in that the H_2CO_3 is diminished. Unless compensated by a decrease in the BHCO_3 , the ratio 1:20 is decreased, the pII rises, and an uncompensated alkalosis results.

To compensate for the abnormal loss of carbon dioxide through the lungs, there has to be a loss of BHCO_3 . This is thought to be accomplished by an increase in the chloride ions. The increased chloride retention diminishes the residual base present for combination with HCO_3^- to form BHCO_3 . It is thought by some that the kidneys preferentially excrete HCO_3^- over Cl^- to accomplish this task.

Some investigators have also noted that there is an increase in plasma lactic acid and ketone bodies which further reduces the BHCO_3 and promotes a more normal pH. An overcompensation of this mechanism would lead to the development of an acidosis as has been reported. As hyperpnea would also be present in this condition, it is evident that the pH of the blood must be known before treatment with alkalis is instituted.

Since the bulk of the salicylates are excreted in the urine, the treatment is directed toward increasing the renal output. Another factor to be considered in the treatment is the administration of the chlorides for union with the base present. Both of these can be accomplished by the administration of adequate amounts of glucose in normal saline. Oxygen administration as well as other supportive measures should be followed out. Morphine or barbiturates have been used by some to slow the respiratory rate and thus diminish the loss of carbon dioxide from the lungs. Vitamin K and ascorbic acid are used to diminish the hemorrhagic manifestations.

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Psychologic Aspects of Pediatrics

MENTAL TESTING IN CHILDREN

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PSYCHOLOGIC testing, originally developed by Binet in 1905 to measure mental capacity, has been greatly extended within recent years and tests are now available for measuring innumerable psychologic attributes. Thus there are tests for measuring emotional stability, emotional interests, masculinity-femininity, social intelligence, honesty, social attitudes, scholastic interests, special abilities, educational achievement, and various personality traits. The tests which are of special interest to the physician are those which relate to mental functioning.

Psychologic testing of children should be discouraged except where a specific indication exists. There is no more reason for determining the intelligence quotient in a normal child than in estimating the basal metabolic rate, and there are disadvantages. A numerical rating of intelligence has only relative accuracy. By permitting seemingly precise comparisons, it encourages an attitude of competition among mothers and may lead to needless parental concern, disappointment, and anxiety. There are, however, occasional instances of doubtful intelligence where testing is indicated. The physician should therefore familiarize himself with the uses and limitations of this technique. He should be able to interpret the results of tests in a general way and understand the degree of reliability and validity with which these interpretations are made.

INDICATIONS FOR MENTAL TESTING

1. *Doubtful Intelligence.*—Intelligence testing is useful in detecting retarded mentality in doubtful cases. In addition, it gives a measure of the extent of the deficiency and shows how it affects the child's adjustment in other respects. Children who make little use of their capabilities because of emotional blocking and who are, as a result, erroneously considered to be defective can be recognized in this way.

2. *Behavior Problems.*—Where the difficulty appears to be an outright behavior problem it is often desirable to have an appraisal of the child's intellectual status in order to ascertain whether this factor is aggravating the total behavioral picture.

3. *Educational Retardation.*—In appraising a child who is doing poorly at school the relationship between all factors complicating the patient's adjustment should be made. This includes testing not only for intelligence but for special disabilities (reading, arithmetic, spelling, etc.) and personality as well.

4. *Diagnostic Problems.*—Mental testing is helpful in differentiating mental deficiency per se from that associated with organic defect, a psychosis, or a com-

bination of these. For this purpose intelligence tests should be supplemented by personality tests. Feeble-minded children score uniformly low, i.e., the retardation in mental development is widespread, relating to all the mental faculties. Where the mental defect is organic or psychotic in origin the scatter of test results is likely to be wide. For example the child may be able to give only a 4-year response on certain tests but on others may score 8 or 10 years.

5. *Effect of Therapy.*—Mental testing is helpful in offering a baseline against which the effects of various types of therapy, such as educational tutoring, medication, e.g., glutamic acid, benzedrine, hormonal therapy, (as thyroid extract) or psychotherapy can be measured.

6. *Miscellaneous Uses.*—Mental testing has been found useful in child adoption, vocational guidance, in the appraisal of aptitudes, in work with juvenile delinquents, in the investigation of mental growth, in research on individual differences, and in the study of the relation between intellectual and personality factors and physical handicaps, as poor vision, poor hearing, disturbances of the nervous system.

In mental testing the individual's performance in many different functions is measured. Failure or success in any one mental function may be of only slight significance for classifying an individual, since correlation between the mental functions varies widely. Success in music, representative drawing, and mechanical ability, for example, are relatively independent and correlate poorly. On the other hand, reading ability and aptitude in arithmetic are fairly closely but not perfectly correlated with general competence, while spelling is not readily predictable from general school grading.

Mental testing cannot be expected to measure pure native capacity for intellectual accomplishment. It indicates the immediate efficiency of the individual in certain specific respects. The results of intelligence tests are relative, i.e., the score which the child makes has significance only by comparison with the scores of other children on the same test. The score serves as an indication of the rank of the individual in a group in which he may be placed or with which he may be compared. What is being measured is the reaction of the innate endowment of the child to his training at the moment when he is being tested. The particular activities demanded of the individual being tested are selected from those which are likely to be common to the experience of all the persons who are to be compared.

Like other laboratory procedures, psychologic tests depend for their reliability not only on the accuracy with which they are standardized but also on their proper administration, scoring, and interpretation. In addition, the wholehearted cooperation of the child being tested must be obtained and the subject must be representative of the populations used originally in standardizing the test in regard to age, sex, educational level, and cultural background.

Norms for intelligence are based upon the child's ability to perform prescribed tests in a prescribed manner at certain stated ages. By mental age is meant "that degree of general mental ability which is possessed by the average child of corresponding chronologic age" (Terman). The score obtained by

adding up credits which the child received for all age levels is referred to as the mental age (M.A.). The ratio of mental age to chronologic age (C.A.), multiplied by 100, gives the intelligence quotient (I.Q.) The basal age (B.A.) is the highest age level at which all the tests are passed. The table below gives the range of intelligence quotients in children of a "normal" population.

RANGE OF INTELLIGENCE QUOTIENTS IN CHILDREN

	I. Q.	PERCENTAGE IN POPULATION	CLINICAL DIAGNOSIS
Inferior intelligence	Below 70	1	Mentally deficient
	70-79	5	Borderline
Normal range	80-89	14	Dull
	90-99	30	Average or Normal
	100-109	30	Average or Normal
	110-119	14	Bright
Superior intelligence	120-129	5	Very bright
	130 and over	1	Gifted
	150 and over	0.1	"Genius"

The average I.Q. is close to 100 with a standard deviation of 16 points. The error in the usual test is about 5 points either way.

The limitations of the I.Q. are as follows:

1. Its validity does not extend beyond the validity of the scales used.
2. It does not take into account special abilities or disabilities.
3. It may put a premium on certain abilities depending upon the test used.
4. Caution is necessary in interpreting intelligence test scores since different tests may yield different results, while the subject's relative position on the normal curve remains undisturbed. That is, a subject's clinical diagnosis may alter on the basis of an I.Q. computed as a result of findings, but his actual capacity has not changed. One test may stress memory, another comprehension, and a third verbalization, so that the child will score higher on the test which emphasizes his own special abilities. It is erroneous to assume that an I.Q. obtained on one test will be identical with the I.Q. obtained on another and therefore the test administered must always be considered.

TYPES OF MENTAL TESTS

Mental testing was introduced by Alfred Binet in 1905. With his co-worker, Simon, he submitted a large number of questions and tasks to children of various ages and capabilities. By the simple yet original device of grouping the tasks according to age, he was able to estimate the mental capacity of children from the number of tests which were successfully performed at each age level. Since Binet's time the tests have been simplified. At present the revision of the Stanford-Binet test, introduced by Terman and Merrill¹ in 1937, is most widely used.

Terman and Merrill Revision of the Stanford-Binet Scale (1937).—This test is designed to measure various mental faculties such as memory, reasoning power, judgment, grasp of general information. Thus, children at 2 years of age are expected to be able to insert insets (a square, circle, and triangle) into a form board; to identify certain objects by name such as a button, a thimble,

a cup, and the like; to identify various parts of the body; to build blocks, etc. Later on, for example at 5 years, the child is expected to complete an incomplete drawing of a man; to fold paper in the form of a triangle; to give simple definitions of words such as "ball," "bat," "stone"; to copy a square; to memorize sentences, etc. At 10 years, the child should be able to define certain words; he should be able to recognize absurd situations in pictures which are shown to him; he should be able to repeat six digits, etc.

Wechsler-Bellevue Adult and Adolescent Scales.—The tests developed by Wechsler² are suitable for subjects ranging in age from 10 to 60 years. The scales are divided into ten subtests, five verbal, yielding a separate Verbal I.Q. and five nonverbal yielding a Performance I.Q.; the two scales combined furnish the examiner with a General I.Q. The verbal scale consists of general information items; a comprehension test consisting of questions such as, "Why should people pay taxes?" "Why are laws necessary?" arithmetical reasoning problems ranging from simple addition to more complex calculations like: "If a train goes 150 yards in ten seconds, how many feet can it go in one-fifth of a second?"; a test of similarities wherein the subject is asked to state in what way two things are the same or alike, e.g., orange—banana, coat—dress, etc.; and a memory for digits test, in which the subject's ability to repeat various sequences of digits forward and backward is tested. The Performance Scale consists of a completion test wherein the subject points out an important deletion from a series of fifteen pictures; a picture arrangements test consisting of several series of cartoonlike pictures which are presented to the subject in a mixed order which he has to place in correct sequence; an object assembly test which presents the subject with three separate dismembered items which he has to put together properly; a block design test which presents different designs which the subject has to duplicate with colored cube blocks; and a digit symbol test which requires the subject to substitute symbols for numbers from a code consisting of nine numbers each with a different symbol.

The chief advantages claimed for the Bellevue Scales are:

- a. The material is well-suited for the testing of adolescents and adults.
- b. An individual's performance is compared with the average of his own age group.
- c. The full scale gives appropriate weight to performance and verbal tasks.
- d. The test results agree better with clinical judgments than those obtained from other general intelligence tests.
- e. The test is an aid in diagnosis since factors that may be contributing to emotional maladjustment can be uncovered. Thus, this test not only offers objective quantitative results but it is useful qualitatively as an aid in differentiating between "normal," psychoneurotic, psychotic, and organically determined behavior.

The Bellevue Scales have been administered extensively to both children and adults. Because of their construction and statistical bases the I.Q.'s which they yield are often in variance with the I.Q.'s obtained for the same subject whose Binet I.Q. is known. Weider, Levi, and Risch³ have constructed tables

that equate the two I.Q.'s and show that the subject's relative position does not change although the I.Q. designating this position results in a different numerical figure.

Testing During the First Two Years.—Intelligence during the first few years of life cannot be as accurately measured as at later ages but tests have been devised by which infants may be classified as backward, dull normal, average, or advanced.⁴ Since tests in infants are largely dependent on motor ability, a careful physical examination with particular attention to muscle tonus and coordination should precede the tests. The difficulty in recognizing spastic diplegia and basilar ganglion lesions in young infants is well known. Myotonias which interfere with motor performance are occasionally seen. Estimates of intelligence in infants with mild or even moderate degrees of hydrocephalus should be made with caution.

Testing during early life is useful where adoption is contemplated and this procedure is now used by many agencies. The tests require more time and practice than most physicians are able to devote to them; nevertheless we should be acquainted with the character of the tests used and with the reliability of the results. The tests frequently applied in office practice such as the age of smiling or sitting up are of little value because they are not standardized and the normal variability is wide.

In 1925 Gesell⁵ published his Developmental Inventories, which established norms for mental and motor growth during the preschool period. More recently, Gesell and Amatruda⁶ published a more complete developmental schedule from four weeks through five years. The tests reveal not only mental retardation but emotional instability, defects in vision, in hearing, and in motor ability. The effects of cerebral injury can be distinguished from signs of amentia within the first year.

According to Gesell practically every case of mental deficiency can be recognized in the first year of life except for the small number of exceptional cases arising from secondary causes later on. This is best done by a progressive appraisal of the child's maturity status from time to time. The criteria used by Gesell are the young child's command of his body postures in the supine, prone, sitting, and standing positions; his ability to roll, creep, walk, and run; his discriminating regard for sights and sounds; his ability to grasp, manipulate, and release objects; his ability to exploit his environment in a varied and increasingly elaborate manner; his propensity to learn and profit by experience; his power to communicate with his social environment by visual following, by intent and regard, by gestures, vocalizations, and words; his discriminating regard for persons; his capacity to assimilate the culture into which he was born.

The Gesell tests are designed to disclose the four basic fields of behavior: motor, adaptive, language, and personal-social behavior. The results are expressed as D.Q. or Developmental Quotient, rather than as I.Q. The D.Q. is the ratio between the maturity age and the chronologic age. Gesell considers the D.Q. more discriminating than the I.Q. since the D.Q. can be specifically ascertained for each field of behavior and for individual behavior traits.⁷

Goodenough Draw-A-Man-Test^a.—This test is simple to administer, it requires no special material and it generally holds the child's interest. Moreover it is possible to learn much about a child's problems from his drawing and from his own interpretation of it.

The examiner asks the child to draw a man. He is urged to draw it carefully, in the best way he knows how and to take his time. The test is highly reliable, correlating well with the Binet tests. The test is most suitable for children between 3 and 10 years of age.

The child receives one point for each of the items which is present in his drawing. For each 4 points one year is added to the basal age which is 3 years. Thus if the child's drawing shows that the first nine items are present in his drawing he scores 9 points and his mental age score is 3 plus $\frac{9}{4} = 5\frac{1}{4}$ years.

Method of Scoring the Goodenough Draw-a-Man Test^a

1. Head present.
2. Legs present.
3. Arms present.
4. Trunk present.
5. Length of trunk greater than breadth.
6. Shoulder indicated.
7. Both arms and legs attached to trunk.
8. Legs attached to trunk and arms to trunk at correct point.
9. Neck present.
10. Outline of neck continuous with that of head or trunk or both.
11. Eyes present.
12. Nose present.
13. Mouth present.
14. Both nose and mouth in two dimensions; two lips shown.
15. Nostrils indicated.
16. Hair shown.
17. Hair on more than circumference of head, nontransparent, better than scribble.
18. Clothing present.
19. Two articles of clothing, nontransparent.
20. Entire drawing, with sleeves and trousers shown, free from transparency.
21. Four or more articles of clothing definitely indicated.
22. Costume complete without incongruities.
23. Fingers shown.
24. Correct number of fingers shown.
25. Fingers in two dimensions, length greater than breadth, angle subtended not greater than 180 degrees.
26. Opposition of thumbs shown.
27. Hand shown as distinct from fingers or arms.
28. Arm joint shown. Either elbow, shoulder, or both.

PERFORMANCE TESTS

The usual mental tests depend to a large degree on the ability of the child to understand language and to respond orally. Children who are deaf, retarded in the development of speech, or mute, illiterate, or from a home where a foreign

language is spoken are consequently at a distinct disadvantage in the ordinary test. To overcome this difficulty a number of performance tests have been devised which require little or no language ability.

In 1931, Stutsman⁹ published the *Merrill Palmer Performance Tests*, which include tests from 18 to 72 months arranged in six-month groups. These have the advantage over most tests at the preschool level (2 to 3 years) of keeping the child interested. They have a high degree of reliability.

Of considerable value is the *Pintner-Paterson Performance Test*¹⁰ which is suitable for children of 4 to 15 years of age. It includes a great variety of tests and requires very little verbal response. Though it tests facets of mental abilities in a manner different from that used by the Binet tests, it nevertheless correlates closely with the Stanford-Binet intelligence scores.

The *Arthur Point Scale of Performance Test*¹¹ has also enjoyed wide popularity as a performance test where testing with the Binet is either not possible or unreliable. It was first published in 1925 and is most useful for ages 5 to 15 years. As the name suggests, it is primarily a point scale and heavily weighted with manual tasks. It, too, correlates well with the Binet results.

The test is made up of a number of subtests among which is the Sequin Form Board which has insets for ten geometric figures of different shapes. The subject is allowed three trials to fit the figures into the board. The score is the time of the shortest trial. Another is the Healy Picture Completion Test. For this test there is also a kind of form board consisting of a large picture from which ten square holes have been cut. The subject is supplied with fifty pictures of objects pasted on blocks and is expected to insert blocks into the appropriate squares.

TESTING FOR HANDICAPPED CHILDREN

The Binet-Simon Test has been especially restandardized for application to the blind¹² as well as to the deaf.¹³ In the former case the visual material has been modified and adapted for tactual stimulation, and in the latter case pantomime and visual rather than auditory stimulation is used. Whenever possible, performance tests of intelligence and other nonlanguage tests which minimize the need for verbal directions are appropriate for administration to the acquired deaf patient, the mute, the retarded, the reading disabled, the bilingual, and the child from a different culture with difficulty in comprehending the instructions as presented.

GROUP TESTING

Though not new at the time, group intelligence testing developed as a useful instrument from the work done in the U. S. Army during World War I. The Army Group Intelligence Examination Alpha, generally referred to as Army Alpha, consisted of questions designed to measure auditory attention; simple arithmetic problems; items involving common sense or practical judgment; pairs of words to be marked as having the same or different meaning; disarranged sentences to be comprehended and marked true or false; incomplete number series to be completed; verbal analysis; and items calling for general information.

The army tests were found useful in the selection of soldiers and officers for various duties, for advancement and for special training. It served as a ready means for the early identification and elimination of those unfit for military service because of low intelligence.

Numerous revisions of the original army test have been devised and new types of group tests have been introduced for various populations and situations. These group tests are easier to give, they can be machine-scored, and they can be administered to large groups at the same time by practically untrained persons. They have been used in military organizations, schools, industry, civil service, prisons, and the like.

SOURCES OF ERROR

In order to obtain reliable information from an intelligence test certain criteria must be met:

(1) The wholehearted cooperation of the child must be obtained, otherwise the score will be too low. This occurs also if the child is fatigued, ill, or unmotivated.

(2) The instructions must be followed rigidly by the examiner.

(3) The technique of scoring must be closely adhered to. Special psychologic training is necessary for the administration of tests and for the interpretation of results. Some of these tests are scored by grade or by percentile ranking rather than by I.Q., thus making interpretations more complex and requiring extra caution.

While a numerical rating is helpful in many situations, a qualitative appraisal of the results yields significant information which should be taken into consideration. Such factors usually shed light on the child's behavior, thought processes, social, emotional; and interpersonal relationships with parents, siblings, and school chums. While these latter factors are more reliably ascertained through the use of procedures specifically designed for these purposes (tests of personality), observation and attention to the child's approach to material, conversation, cues, etc. yield valuable information during intelligence testing.

At best, intelligence tests merely sample a few aspects of the complex, multi-determined human factor which we call intelligence. The objective character of the results obtained enables comparisons to be made with norms that have been standardized. While this procedure is far better than a subjective, biased, unstandardized appraisal, caution must be exercised not to overemphasize the quantitative features of the I.Q.

FACTORS INFLUENCING INTELLIGENCE TEST RESULTS

Sex has only a slight influence on the mean scores, but boys are somewhat more variable than girls. Children of superior social status average considerably above children from an inferior environment. The order among siblings appears to affect the I.Q. only in so far as first-born children rank as gifted children more often than later-born. Superior intelligence is uncommon in twins. Bilingualism has little effect after the first three or four years of school.¹⁴

Race and nationality influence the I.Q. but it is not clear whether the differences found are dependent primarily on hereditary or environmental factors. The highest average scores are obtained by children of English, Scottish, and Jewish descent. In all studies made in the United States, Italian and Polish children average uniformly low, but they achieve somewhat higher scores on nonlanguage tests than on those requiring more knowledge of English. On practically all tests Negroes are inferior in I.Q. to white children as a whole but they test somewhat higher than Italian and Polish children. The average I.Q. for Negro children tends to decrease as the age and grade increases and this has been interpreted to indicate the adverse effect of poor environment on the child. Studies indicate that less than 25 per cent of Negro children reach or exceed the median of white children. Chinese children in the United States test fairly high. Indian children score low, specially pure-blooded Indians, but Jamieson and Sandiford found they reached almost average level on certain tests not involving the understanding of the English language. It is probable that the tests used do not give a fair estimate of their ability because these children have lived in a different environment and have had different experiences than the white children for whom the tests are standardized. It should be clearly understood that in all racial and national groups there are individuals who test high, only the average or mean scores differing. It is impossible at present to estimate the intelligence of children in their native countries from these results, as immigration to the United States involves a highly selective factor.

Rural children score lower than city children. This difference decreases with the number of years of school attendance, indicating that at least part of the handicap is due to inadequate education and training.

Yerkes¹⁵ found that, during the first World War soldiers from the Northern section of the country scored higher than those from the South. Race cannot account for this difference since the same results were obtained for both whites and Negroes. Possibly education was the important factor. Great differences were found between the average for soldiers from Oregon and from Mississippi; as great, in fact, as those found between Indians and whites. This wide variation is difficult to explain.

According to several observers the administration of Benzedrine leads to an improvement in performance on intelligence tests in most children. This probably results from an induced feeling of well-being, an increase in confidence and energy, greater alertness, and a greater desire to succeed.¹⁶

Infants born prematurely are somewhat inferior to full-term infants during the first year of life. This is less pronounced if correction is made for the time of prematurity. Smaller infants are more retarded than larger ones. On the average, infants with birth weight under 4 pounds (1.8 kg.) do not reach the average development of full-term children until the eighteenth month, whereas infants weighing more than 4 pounds overtake the normal group at about 9 months of age. Prematurely born infants are more retarded in motor and manipulative development than in intellectual content and social responsiveness.¹⁷ In personal social behavior, as tested by the Gesell Developmental Inventories,

the performance of prematurely born infants was consistently relatively superior to full-term infants when account was taken of the amount of prematurity. This has been attributed to the unusual care and attention offered the prematurely born, to their closer association with adults, and to the fact that they have had an additional extrauterine period and therefore greater opportunity for training. At a later age the prematurely born give average scores on language tests which would make them somewhat superior if account is taken of the period of prematurity. Children of school age who have been born prematurely are in the majority of instances in the proper grade for their age, and their intelligence is similar to that of full-term children of like age.

Continued severe psychic trauma such as life in an undesirable institution or exposure to an unstimulating environment in the home leads to a decrease in the I.Q. in young children. Conversely, children reared in superior foster homes show higher I.Q.'s than might be expected from their original heredity and environment. Studies of identical twins reared apart have shown that the greater the difference in environment the greater the difference in I.Q. One must conclude from these studies that "extreme differences in educational and social environments are accompanied by significant differences in intelligence."¹⁸

Intelligence Resemblance in Families.—There is on the whole, a fairly close resemblance in the I.Q.'s of members of the same family (represented by a correlation coefficient of about .50). The resemblance between siblings and mother, and siblings and father is of about the same order. Terman found, in his follow-up study of gifted individuals, that the mean I.Q. of their offspring was 127.7. Though this average was about 24 points below that of the parents, it is much higher than that found in the general population. The incidence of children with feeble-minded and borderline mentality was low. On the other hand, the proportion of offspring with I.Q.'s of 150 or higher was twenty-eight times as great as that for unselected children.¹⁹

There is no definite correlation between I.Q. test results and health ratings, history of illnesses, body build, skeletal maturity (as measured by ossification of the bony centers), birth order, being an only child, broken homes, or excessive shyness.

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Comments on Current Literature

BONE INVOLVEMENT IN LEUCEMIA

PAIN along the bones and in the joints in the acute leucemias has not been stressed sufficiently. Similarities of symptomatology in leucemia and rheumatic fever have led to confusion and to real diagnostic difficulties. The co-existence of leucemia and rheumatic fever is regarded as rare. From the standpoint of management and of prognosis, the importance of early correct diagnosis is appreciated readily.

Aisner and Hoxie¹ in the *New England Journal of Medicine* for May 20, 1948, have reviewed pertinent material on this subject and have added four interesting cases of their own. They call attention to the fact that as early as 1889 Ebstein, and, in 1895, Fraenkel, considered pain and tenderness along the bones and in the joints a prominent feature of the symptomatology of leucemia. Since that time a number of writers on leucemia have emphasized this clinical point. In two of the four cases reported by Aisner and Hoxie, in which bone and joint manifestations were outstanding features, a diagnosis of acute rheumatic fever was made on admission to the hospital. In the third of the four cases, a diagnosis of subacute bacterial endocarditis had been made before admission, and in the fourth, the referring physician had diagnosed the case as rheumatic fever. Even early blood studies may be confusing since the blood picture of early leucemia may be within normal limits, and since nonleucemic children may produce immature white blood cells in response to severe infections. Bone marrow studies also may be nonrevealing in early leucemia.

The presence or absence of leucocytosis may be of some diagnostic aid, since leucocytosis is of general occurrence in active rheumatic fever associated with joint pain. According to Wilson² the white blood cell count varies between 8,000 and 23,000 and in 91 per cent of her cases the white blood cell counts were over 9,000. In this connection Aisner and Hoxie stress the differential count, stating that "leucopenia associated with symptoms referable to the bones and joints should make one suspect conditions other than acute rheumatic fever."

In rheumatic fever the differential count reveals an increase in the percentage of neutrophils. Consequently the occurrence of lymphocytosis, especially when associated with leucopenia, suggests a diagnosis other than rheumatic fever. Two of the cases described by Aisner and Hoxie illustrate these clinical points. In discussing joint pain, these authors state that in conditions like leucemia in which there may be considerable destruction of blood elements and the liberation of nucleoprotein, the blood uric acid level may be elevated and this value in itself may be used as a differential diagnostic feature.

In a brief discussion of the x-ray appearance of the bones and joints in leucemia, these authors emphasize the wide variability in the roentgenologic aspects of the skeleton in leucemia. Changes in the bones may include subperiosteal elevation, cortical destruction, rarefaction, osteosclerosis and osteoporosis, the most common skeletal finding being periosteal elevation.

In the June (1948) issue of the *American Journal of Roentgenology and Radium Therapy*, Frederic N. Silverman³ presents an extensive study of skeletal lesions in leucemia. In this report which carries a review of the literature, and is based on observations on 103 infants and children, Silverman states

that accurate diagnosis of leucemia in the pediatric subject which is often difficult, is aided considerably by roentgenologic studies of the skeleton. Silverman studied 131 patients with leucemia, on 103 of whom the roentgenologic studies were considered adequate. Fifty-two of the 103 leucemic children showed bone changes and four types of lesions were observed: transverse bands of diminished density, osteolysis, osteosclerosis, and subperiosteal new bone formation. Of forty-two patients who complained of bone pain, twenty-five had skeletal lesions demonstrable in roentgenograms.

In discussing differential diagnosis, Silverman states that in his experience the conditions most frequently confused with leucemia were, first, rheumatic fever, and second, secondary anemia. Still's disease and infectious mononucleosis were among the diagnoses considered in certain cases of leucemia. In his conclusion Silverman states that children showing anemia, fever, and pain in the extremities present a problem in differential diagnosis, and that the roentgen method often proves an aid in the diagnosis of acute leucemia.

In addition to rheumatic fever and leucemia, differential diagnosis of patients with bone and joint pain, particularly those in the pediatric age group, must include such conditions as undulant fever, poliomyelitis, osteomyelitis, scurvy, rickets, syphilis, gonorrhea, tuberculosis, Haverhill fever, Hodgkin's disease, and Still's disease. It is of great importance that, in addition to routine and careful examinations of the blood, all patients presenting bone and joint pain as symptoms should have careful x-ray studies in order to detect changes in the skeletal system.

RUSSELL J. BLATTNER

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News and Notes

Dr. James Goodfriend, Instructor of Pediatrics at Washington University Medical School, died of a heart attack Monday night, July 5, 1948.

Dr. John Aikman of Rochester, New York, died July 13, 1948.

Dr. Osear Reiss of Los Angeles died suddenly on June 16, 1948, as he was preparing to leave for Chicago to preside at the meetings of the Section on Pediatrics of the A. M. A. of which he was chairman.

At the A. M. A. meeting of the House of Delegates in Chicago, on June 21, the Distinguished Service Medal of American Medical Association was awarded to Dr. Isaac Arthur Abt. In honoring Dr. Abt for his lifetime of service to American Medicine, the Association has paid a well-deserved tribute to an outstanding pediatrician who is loved and respected by all.

The following were certified by the American Board of Pediatrics at the examination in Chicago, June 26 and 27, 1948:

- Dr. John H. Cordes, Jr., 216 Empire Bldg., 302 Central Avenue, St. Petersburg, Fla.
- Dr. Victor J. Cordes, 7405 Harwood Avenue, Wauwatosa 13, Wis.
- Dr. Susan Coons Dees, Duke Hospital, Durham, N. C.
- Dr. Harold X. Gerber, 1046 Wilson Avenue, Chicago 40, Ill.
- Dr. John Roland Harvin, 206 North Sumter Avenue, Sumter, S. C.
- Dr. Maurice Kaufmann, 2 Nassau Place, Hemstead, N. Y.
- Dr. John T. Kometani, Tulane Medical School, Dept. of Pediatrics, New Orleans, La.
- Dr. William Caldwell Layton, 2300 Ralston Avenue, Burlingame, Calif.
- Dr. Jacob S. Light, 405 37th Place, S.E., Washington 19, D. C.
- Dr. Bernard L. Lipman, Medical Arts Building, Philadelphia, Pa.
- Dr. Dan Campbell McDougall, 210 Kane Building, Pocatello, Idaho.
- Dr. Irving Howard Mauss, 443 Beach-138th Street, Belle Harbor, N. Y.
- Dr. Evelyn E. Miller, 1642 Harrison Street, Philadelphia 24, Pa.
- Dr. Dominic S. Motsay, 111 West Lockhart Street, Sayre, Pa.
- Dr. Brian St. John Moynahan, 334 Washington Avenue, Belleville, N. J.
- Dr. Harry Thomas Nagel, 518 South 5th Avenue, Maywood, Ill.
- Dr. Louis J. Needels, 402 Loma Alta Drive, Santa Barbara, Calif.
- Dr. Phyllis T. Mrazek Orland, 6628 West Cermak Road, Berwyn, Ill.
- Dr. Herbert J. Palmer, 170 West 77th Street, New York City, N. Y.
- Dr. John Lyman Peek, Johns Hopkins Hospital, Baltimore 5, Md.
- Dr. Walter Pick, 42 Fox Street, Fitchburg, Mass.
- Dr. Bernard C. Prietsch, 4752 Baldwin Manor Road, Pittsburgh, Pa.
- Dr. Francis Lupton Robinson, Permanente Foundation Hospital, 280 MacArthur Blvd., West Oakland, Calif.
- Dr. Joseph L. Rubel, 5 East Gregory, Pensacola, Fla.
- Dr. Henrietta K. Sachs, 1820 Juneway Terrace, Chicago 26, Ill.
- Dr. Joe M. Standefer, 934 42nd Street, Des Moines, Iowa.
- Dr. Meritt W. Stark, Child Research Council, 4200 East 9th Avenue, Denver, Colo.
- Dr. Walter Milton Tasem, 619 South Bonne Brac, Los Angeles, Calif.
- Dr. Herbert Allan Wenner, University of Kansas Hospitals, Kansas City, Kan.
- Dr. Norman C. Woody, Jr., 1430 Tulane Avenue, New Orleans 13, La.
- Dr. Charles Richard Yoder, 705½ East Walnut Street, Bloomington, Ill.

At the meeting of the Section on Pediatrics of the A. M. A. in Chicago in June, the following officers were elected for 1948-1949:

Chairman: Woodruff L. Crawford, Rockford, Ill.

Vice Chairman: Ambrose McGee, Richmond, Va.

Secretary: Margaret M. Nicholson, Washington, D. C.

Public health reports up to the last week of June show a definite increase in the incidence in poliomyelitis. As of July 10, 2,533 cases have been reported since the seasonal low week (the third week of March), as contrasted with 1,696 in 1946, and a five year median of 1,027. The disease is in definite epidemic form in the widely separated states of North Carolina, Texas, and California. The New England area shows the lowest incidence as of July 1.

The Nineteenth Annual Postgraduate Symposium on Heart Disease of the San Francisco Tuberculosis Association will be held Oct. 27 to 30, 1948, at the St. Francis Hotel. The session on Wednesday afternoon, October 27, will discuss Heart Disease in Children. Eight papers will be presented by California pediatricians on the subject of rheumatism and operable congenital heart disease.

Dr. James N. Etteldorf has been appointed associate professor of pediatrics at the University of Tennessee Medical College at Memphis. He will be director of the pediatric research and diagnostic laboratory of the Gaston Hospital.

The University of Colorado School of Medicine and the Colorado State Department of Health announce a short course for physicians on problems of newborn infants, both pre-mature and full term, to be given at the University of Colorado Medical Center, Denver, Oct. 14 to 16, 1948, inclusive. The course is open to graduates of medical schools approved by the A. M. A. A registration fee of ten dollars (\$10.00) is required. Inquiries should be directed to Frode Jensen, M.D., Director of Graduate and Postgraduate Education, University of Colorado Medical Center, Denver, Colo.

Book Reviews

Fundamentals of Human Reproduction. Edith L. Potter, M.D., New York, 1948, McGraw-Hill Book Co., Inc., 231 pages.

This concise book describing the background and embryology of human reproduction is well written. Its completeness affords an over-all picture of the course of events leading to the birth of the full-term baby, with the greatest emphasis on the cytology, biology, and embryology of the fetus.

There are three main divisions, of which the first two describe the general background and plan of the reproductive process, and the third is a detailed study of fetal organ embryology. There is a short fourth division pertinent to the birth and future life of the infant.

One of the outstanding features of the book is twelve beautiful black and white plates of fetal development ranging from the chorionic vesicle stage to total body x-radiography of the fetal skeleton. In addition, the diagrammatic illustrations accompanying the text are particularly commendable.

It would seem that the material is too exhaustively covered for this book to be used as a text for basic students of nursing, and that the real value of Dr. Potter's work will be for postgraduate students of nursing and nursing instruction, as well as for medical students, physicians, and students specializing in the field of embryology. MONAT.

Widening Horizons in Medical Education. A Study of the Teaching of Social and Environmental Factors in Medicine, 1948, The Commonwealth Fund, 228 pages. Price \$2.75.

This is the report of a joint committee of the Association of American Medical Colleges and the American Association of Medical Social Workers, with Jean A. Curran, M.D., and Eleanor Cockerill as cochairmen. It is indicative of an important trend away from the purely technical and materialistic character of medical education which has dominated the medical school curriculum in the past twenty-five years, a situation which resulted from the tremendous advances in medical science and techniques during this period.

The committee visited and studied carefully the work in thirteen schools, and obtained from the others, by letter, information as to the extent which consideration of the social and environmental factors enters into the medical curriculum. Although there was no uniformity found in the method of approach or the extent or place of socioenvironmental teaching, it is most important and interesting to find that although the study took place during the accelerated period of medical teaching when the faculties were carrying an extraordinary teaching load, nearly every school was attempting to introduce instruction in this phase of medicine into the curriculum. Details are given of the methods used in many of the schools and of the special projects that have been set up by some. It is obvious from the report that the method of instruction is in a highly experimental state, and the report is of great value in showing what the different schools are doing. Undoubtedly in a few years experience will be gained as to how the subject can best be presented to the medical student. The report very wisely does not attempt to lay down any specific plans as to how this type of instruction should be carried out. The report is largely a description of what is being done in a number of schools and the recommendations and conclusions are general in nature.

It is refreshing to find that so many teachers in our medical schools are becoming interested in the patient as a human being subject to social and environmental conditions and stresses which play a most important role in his health and in the development and treatment of disease conditions. It is a thing the man in practice has learned from experience. It augurs well for the physician of the future that these factors are being integrated into the instruction of the medical student. To the reviewer it would seem as if pediatrics were an ideal place to emphasize the importance of social and environmental factors. It would be of great value to some departments if the part-time teachers were utilized more in developing this aspect of medical instruction, as their recognition of its importance is a very practical one.

B. S. V.

Editor's Column

"THE CRADLE TO THE GRAVE"

IN THE column on the Social Aspects of Medicine the JOURNAL has recently presented two discussions of the British Medical Service Act which went into effect on July 5. Discussions with JOURNAL readers have made it evident that some failed to understand that the discussions covered but one phase of a general social security program, which has been dubbed "the cradle to the grave." The medical part of the program is the most controversial part and naturally is of most interest to JOURNAL readers. In order to give a better understanding of the whole program sponsored by the present labor government in Great Britain, we enumerate some of the nonmedical "benefits" which are an integral part of the Act. Perhaps this will explain to some extent the support the program received despite the opposition of a large part of the British medical practitioners who feel the medical care provisions are unworkable and unfair to physicians.

Sick benefits to workers. \$5.20 a week for a single man, and \$9.90 for a couple with one child.

Maternity allowances. \$32.00 after the birth of a child to an unemployed mother, and \$109.60 to employed mothers.

Children's allowances. \$1.00 a week for each child after the first, regardless of whether the father is employed or unemployed.

Death grants. \$80.00 for funeral expenses.

Industrial injury. \$11.00 a week for single men and more for married couples.

Unemployment benefits for as long as 30 weeks. Single men \$5.20 a week, \$8.40 for a couple, and \$1.50 for the first child.

Old age pensions of \$5.20 a week for women 60 years of age or over and men 65 years of age or over.

These are in addition to free medical and dental care, hospitalization, and surgical and other specialist consultation.

The estimated cost is \$300,000,000 a year, which is three times what the United States spends per capita on its social security program. Compulsory contributions from the wage earners amount to about \$1.00 a week, and 85 cents contributed by the employer. This it is estimated will provide about half of the total cost with the remainder being provided from general revenue funds.

Inadequate facilities to carry out the medical plans will in all probability seriously effect the satisfactory working of the medical aspects of the plans. For example, there are only ten clinics for group practice in London as against an estimated need of 162 for medical care under the Act. From reports it would seem as if the promised free dental care, including dentures, was almost impossible to carry out to the satisfaction of the insured.

British experience with the program during the immediate coming years will be watched closely both by those who favor and by those who oppose the extension of government participation in the field of medical care.

B. S. V.

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Original Communications

THE HEMODYNAMOGRAM: FETAL, NORMAL, AND ABNORMAL BLOOD CIRCULATION DEPICTED BY A NEW METHOD

HAROLD W. BISCHOFF, M.D., FERNANDO R. LEYVA, M.D., AND
E. CLARENCE RICE, M.D.
WASHINGTON, D. C.

THIS method for the depiction of the blood circulation has grown out of a study now being conducted on congenital heart disease at The Children's Hospital, Washington, D. C. With the advent of the newer diagnostic methods now being used in the investigation of congenital cardiac lesions, it was felt that some simple method should be evolved which would readily lend itself to a rapid visualization of the circulatory defects as they were determined. The line diagrams to be presented here have all been constructed from, and pertain to, patients who have come to autopsy at this hospital.

THE NORMAL HEMODYNAMOGRAM

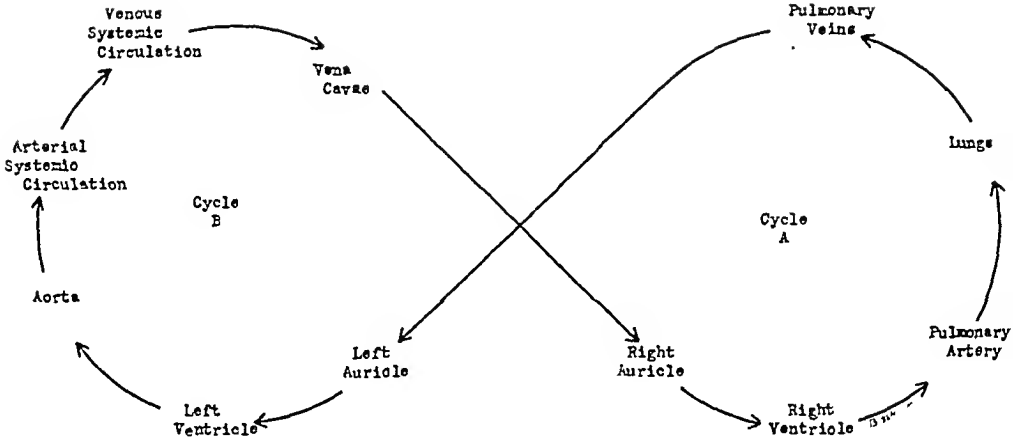
The name hemodynamogram has been arbitrarily assigned to our depiction of the blood circulation, and in this and in all following instances will be referred to as the fetal, normal, or abnormal hemodynamogram. For purposes of simplification, the hemodynamogram has been depicted as a *figure-of-eight*. This is shown in Fig. 1. On inspection of this diagram, it may be seen that the course of blood flow may be followed as a continuous process rather than as two separate circulations. The pulmonary and the systemic circulations have been labeled Cycles "A" and "B" respectively. The whole circulation might just as easily have been represented as one large circle; however, in view of the congenital anomalies encountered, the figure-of-eight pattern is much more easily adapted to simplification of explanation.

FETAL BLOOD CIRCULATION—FETAL HEMODYNAMOGRAM

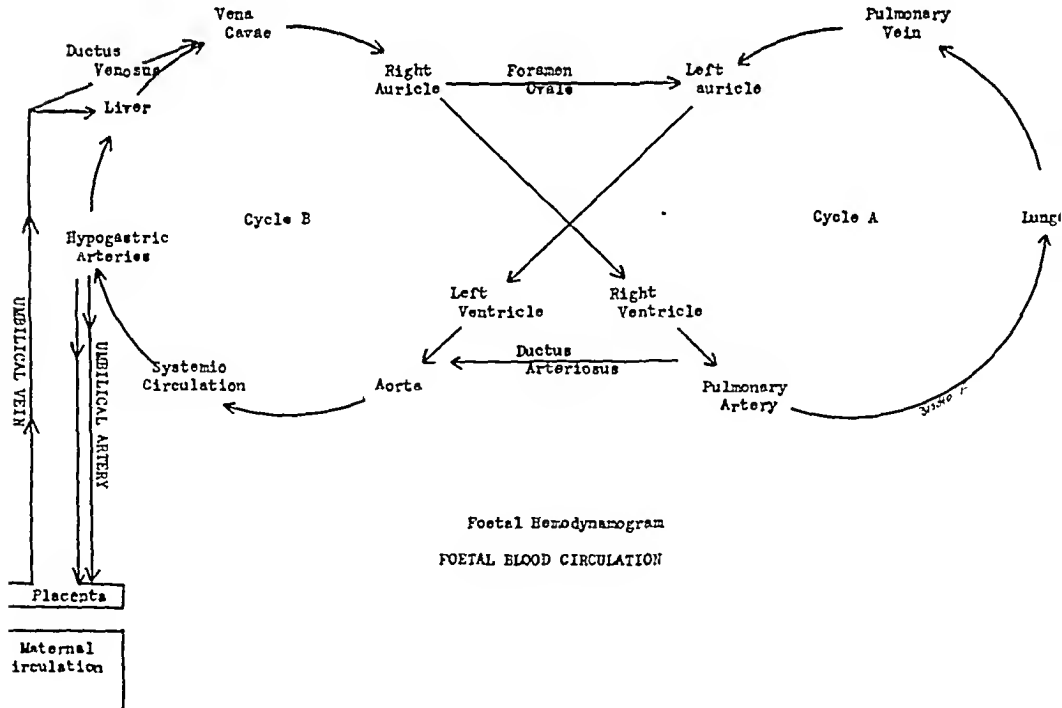
For sake of completeness, there is included a description of the fetal blood circulation before the changes occur which are attendant upon parturition.

As can be seen by an inspection of Fig. 2, the fetal circulation is grossly the same as in the adult with the exception that there are a number of circuitous pathways by which the blood travels in order to circumvent a non-functioning organ (the lung) and to receive oxygen and expel carbon dioxide (placental circulation).

Fig. 1.



Normal Hemodynamogram
NORMAL BLOOD CIRCULATION



Foetal Hemodynamogram
FOETAL BLOOD CIRCULATION

Fig. 2.

A part of the blood coming into the right auricle is passed through the foramen ovale to the left auricle, whence it eventually passes out over the systemic circulation. Upon coming to the common iliac vessels, a portion of the blood is sent to the placenta by way of the hypogastric and umbilical arteries and is returned from the placenta through the umbilical vein. The blood passes mostly to the inferior vena cava through the ductus venosus. A certain proportion of the blood is not passed through the foramen ovale but passes in normal fashion into the pulmonary artery. Shortly after entering the pulmonary artery, the blood encounters another shunt, the ductus arteriosus. By this route blood from the pulmonary artery is sent into the aorta and thence to the systemic circulation.

By these pathways, a minimum of blood is sent through the lungs. The atelectatic or pre-expansive state of the lungs assists in maintaining this circulation by virtue of the resistance offered by narrowed blood capillaries. When birth occurs, the sudden or at least partial expansion of the lung tissue removes the resistance holding back the passage of blood through the lung capillaries, and an approximation to adult circulation is initiated.

Then, granting a normal embryologic development of the septa primum and secundum, with an increased pressure within the left ventricle, the foramen ovale becomes functionally closed.

Christie in 1930¹ reviewed the literature on the closing time of the foramen ovale and the ductus arteriosus and found the statements to be markedly controversial. In a review of consecutive autopsies, excluding all congenitally malformed hearts, he found the closing time of the foramen ovale to be prior to twelve weeks after birth in 87 per cent of 590 normal hearts of infants from one day to one year of age. Likewise he found the closure of the ductus arteriosus to occur prior to eight weeks after birth in 88 per cent of 588 normal hearts of infants from one day to one year of age.

THE ABNORMAL HEMODYNAMOGRAM

In order to demonstrate the clearness of the proposed method, we have included a classical diagram drawn to represent a case of transposition of the great vessels according to the method used by Maude Abbott,² in order that the reader may compare the advantage of the newer method (Fig. 3).

Fig. 4 shows the representation by the hemodynamogram method of transposition of the great vessels. It becomes readily apparent that, by transposition of the great vessels, the systemic and the pulmonary circulations become independent of each other, and were the by-pass defects noted not present, the condition would be entirely incompatible with life.

Patent Ductus Arteriosus (Fig. 5).—The ductus arteriosus originates from the pulmonary artery at the bifurcation of the two main branches and connects with the aorta beyond the origin of the left subclavian artery. In one child who was proved at autopsy to have an Eisenmenger complex³ the left subclavian artery arose from the middle of the ductus arteriosus. That portion of the

ductus which communicated with the left subclavian artery was of the same inside diameter as the latter vessel and opened into the aorta, while the ductus on the pulmonary artery side was entirely occluded.

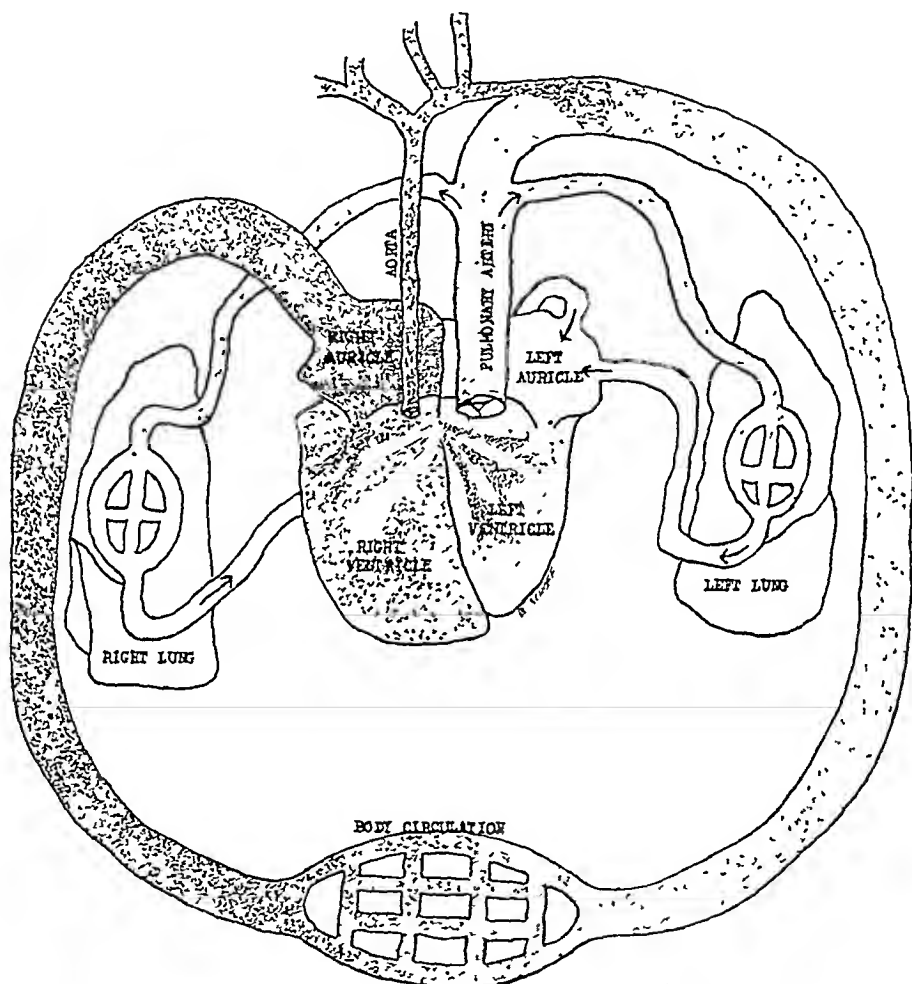
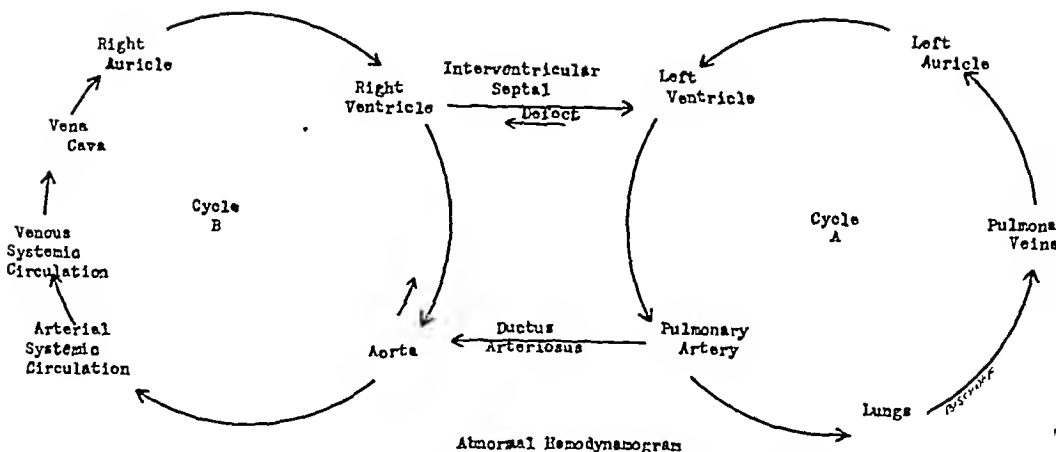


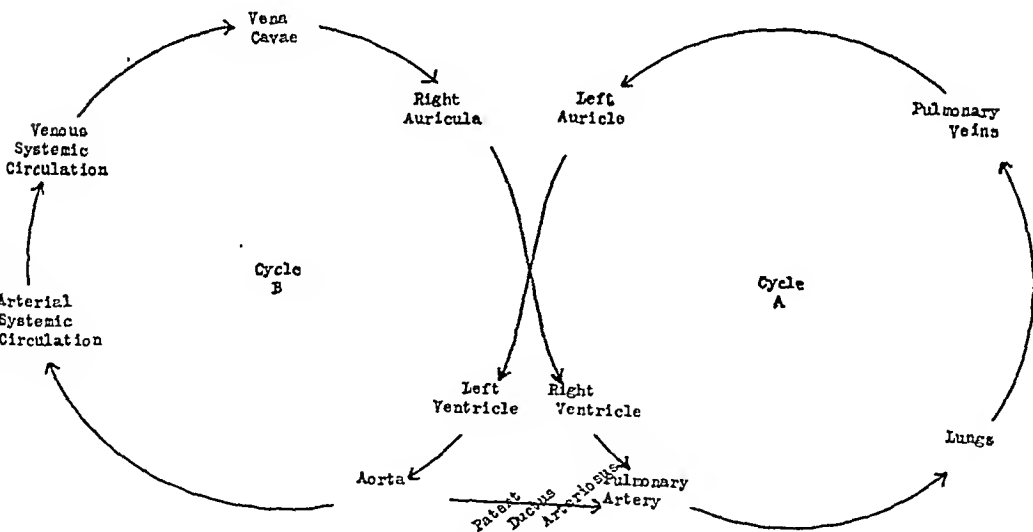
Fig. 3 —Transposition of great vessels, interventricular septal defect, patent ductus arteriosus aortic stenosis

When the ductus arteriosus remains patent, due to the higher pressure in the aorta, blood passes from that vessel into the pulmonary artery. This is represented in Fig. 5 by an arrow passing from Cycle A to Cycle B. Hence oxygenated blood passes from the systemic to the pulmonary circulation, and in the absence of any increased pressure in Cycle B, no cyanosis is produced.

FIG. 4.



BLOOD CIRCULATION IN TRANSPOSITION OF THE GREAT VESSELS WITH PATENT DUCTUS ARTERIOSUS AND INTERVENTRICULAR DEFECT. CASE OF R. W.

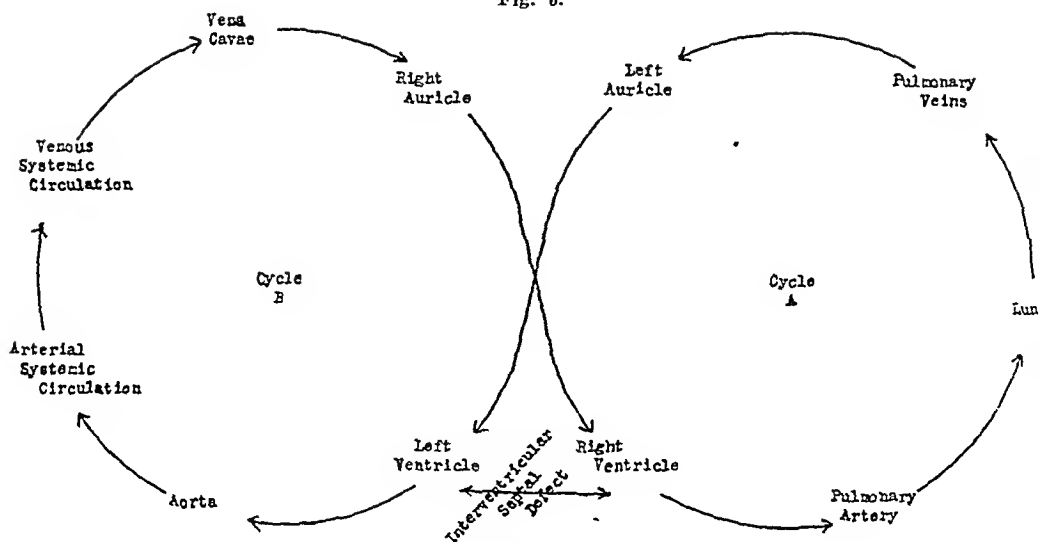


ABNORMAL HEMODYNAMOGRAM
PATENT DUCTUS ARTERIOSUS, CASE OF L. W.

FIG. 5.

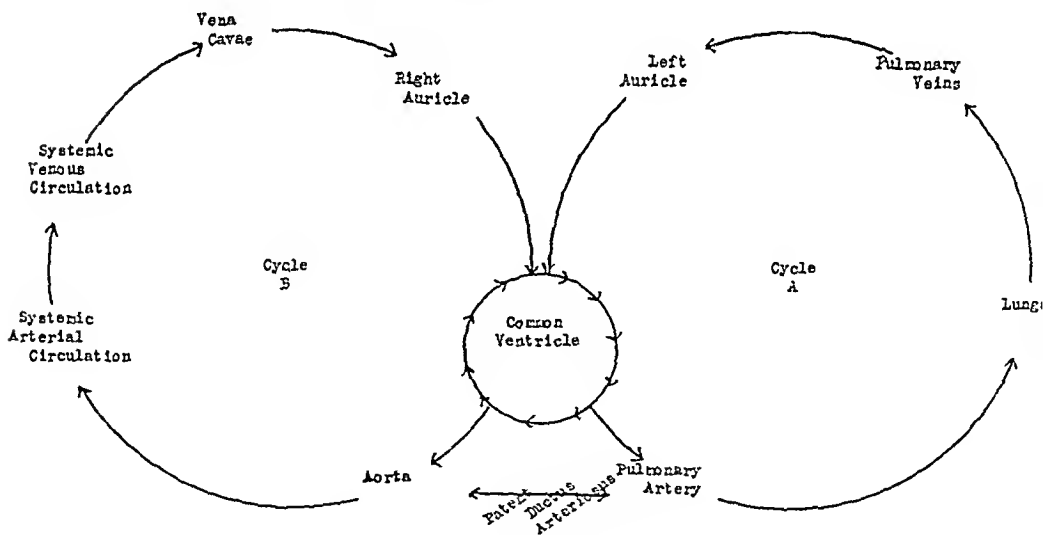
Interventricular Septal Defect (Fig. 6).—In the case of the interventricular septal defect we have almost the same situation as we have with patency of the ductus arteriosus. Here blood is passed from the left ventricle to the right ventricle. As stated by Taussig,⁴ cyanosis never occurs in a *maladie de Roger*, since blood will always pass from an area of high pressure to one in which the pressure is low. We have indicated the flow of blood in both directions only to satisfy the theoretical anatomic possibility of that event.

Fig. 6.



ABNORMAL HEMODYNAMOGRAM

INTERVENTRICULAR SEPTAL DEFECT, BICUSPID AORTIC VALVE, CASE OF H.O.



ABNORMAL HEMODYNAMOGRAM

COR TRILOCULARE BIATRIATUM, PATENT DUCTUS ARTERIOSUS, CASE OF K.B.

Fig. 7.

Cor Triloculare Biatritum (Fig. 7).—In this condition there is mixing of arterial and venous bloods in the common ventricle so that blood reaching the systemic circulation is only partially saturated with oxygen. Blood passing out of the common ventricle would be of the same pressure in both the aorta

and pulmonary artery; hence, although in the case illustrated, a patent ductus arteriosus was present, this would in no way influence the passage of blood from the aorta to the pulmonary artery or vice versa. The arrow depicting the passage of blood between the aorta and pulmonary artery has been drawn to depict the passage of blood in either direction. With presumably identical pressure in both trunks, the passage of blood through the ductus should be subject to variation according to the variations in intrathoracic pressure.

Truncus Arteriosus Communis Persistens (Fig. 8).—The drawing shown in Fig. 8 shows the circulation in two cases of truncus arteriosus communis persistens² in which there were in addition to the common truncus, interauricular septal defects. The arrow between the auricles designates the flow of blood in both directions. In one of our patients there were multiple perforations and in the other the perforation was single. It is rather difficult to believe that in the presence of multiple perforations the flow of blood would be in only one direction, especially since blood would enter both circulations at the same pressure. This equality of pressure must certainly be reflected onward through both Cycles A and B.

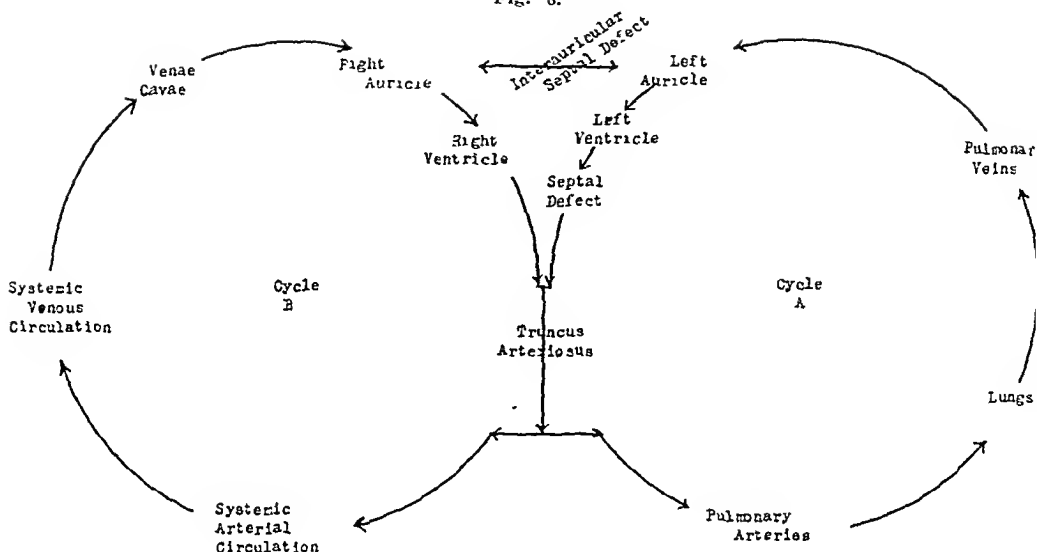
Cor Triloculare Biatritium—Atresia of Pulmonary Artery (Fig. 9).—This figure is similar to Fig. 7; however there is, in addition to the cor triloculare, a patency of the foramen ovale and an atresia of the pulmonary artery. In this child the blood supply to the lungs was effected through the bronchial arteries, which were dilated and tortuous. In this case, the bronchial arteries were much smaller than the aorta. A fluid passing through a smaller tube, or, as in this case, an artery, will pass at a greater rate of speed, and the pressure will drop in proportion to the size of the tube. Considering the latter fact, plus the normal drop in pressure, one would expect blood from Cycle B to enter Cycle A through the patent foramen ovale. The theoretical possibility always remains, however, that blood may pass in either direction; hence the arrow is drawn to depict blood passing in either direction.

Cor Triloculare Biatritium—Mitral Aplasia—Interauricular Septal Defect (Fig. 10).—In this situation we have, in addition to the cor triloculare, a mitral aplasia and a patent ductus arteriosus. Although anatomically a three-chambered heart, functionally it was two-chambered. Due to the mitral aplasia, all blood returning from Cycle A to the left auricle was passed directly into the right auricle by way of the interauricular septal defect. After passing into the common ventricle it was distributed to the aorta and pulmonary artery. With presumably the same pressure in both of the latter vessels, blood might well pass in either direction between them.

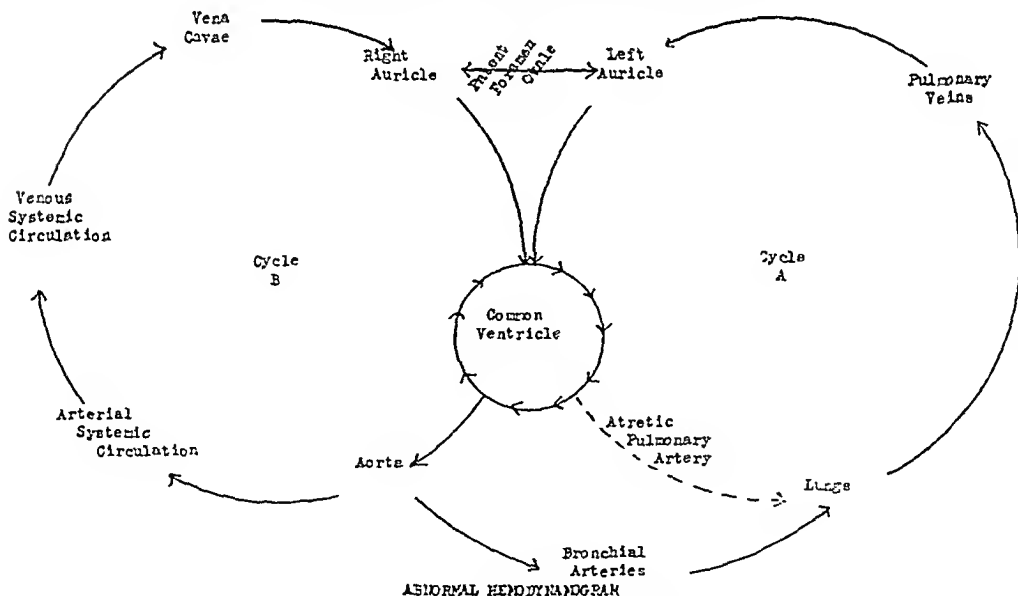
Persistent Ostium Atrioventriculare Commune (Fig. 11).—The last abnormal hemodynamogram to be shown is that of a child with persistent ostium atrioventriculare commune.

In the case illustrated, the interauricular septum came down to the common valve and probably did not allow for any great amount of mixing of blood. However since the defect did exist, during certain stages of the cardiac cycle there must have been mixture of arterial and venous blood. The absence of

Fig. 8.



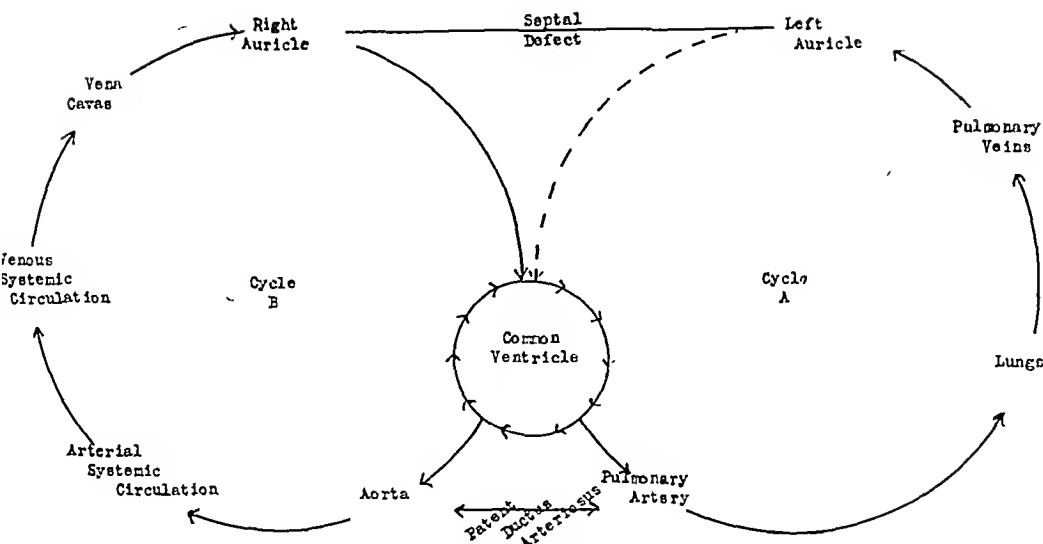
ABNORMAL HEMODYNAMOGRAM
TRUNCUS ARTERIOSUS COMMUNIS PERSISTENS, CLOSED FORAMEN OVALE,
ABSENT DUCTUS ARTERIOSUS, INTERVENTRICULAR SEPTAL DEFECT,
INTERAURICULAR SEPTAL DEFECT. CASES R.M. AND C.S.



ABNORMAL HEMODYNAMOGRAM
COR TRILOCULARE BICAVIATUM, PATENT FORAMEN OVALE,
ATRESIA OF PULMONARY ARTERY, CASE OF J.B.

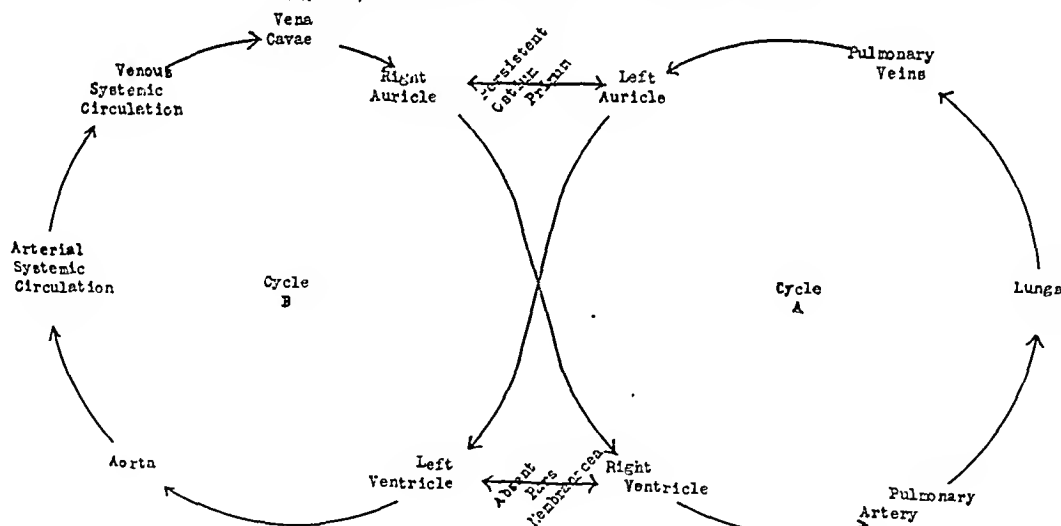
Fig. 9

Fig. 10.



ABNORMAL HEMODYNAMOGRAM

COR TRILOCULARE BIATRIATUM, CLOSED FORAMEN OVALE, INTER-
AURICULAR SEPTAL DEFECT, PATENT DUCTUS ARTERIOSUS, MITRAL
APLASIA, CASE OF C.C.



ABNORMAL HEMODYNAMOGRAM

PERSISTENT OSTIUM ATRIC-VENTRICULARE COMMUNE,
BILOCULATE HEART. CASE OF C.E.J.

Fig. 11.

the pars membranacea gave rise to further possibility for mixing of arterial and venous blood, and since it was of large size, no doubt allowed passage in both directions.

SUMMARY AND CONCLUSIONS

The normal, fetal, and abnormal hemodynamogram is presented. Minor or major differences in the different hearts have required variations in the schematic diagrams presented. The over-all picture of the circulation, however, is represented by a figure-of-eight, with the pulmonary cycle designated as Cycle A and the systemic cycle as Cycle B.

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TRUNCUS ARTERIOSUS COMMUNIS PERSISTENS

A REPORT OF THREE CASES

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THE controversial subject of the requirements which a particular pathologic specimen should meet before it may be classed as a "true" truncus arteriosus has been quite satisfactorily settled by Taussig.¹

Of the three cases to be presented, in two there were four cusps guarding the common trunk, while in the other there were only three. In all three of the cases the coronary arteries arose from the common trunk; in two the pulmonary and the systemic arteries were both derived from the common trunk. In the other case the truncus had been cut off before any of its branches were given off, and it was therefore impossible to determine accurately the ultimate course of the branches.

There was no ductus arteriosus observed in any of the three cases.

The youngest child was 16 days old, the second 2 months, and the oldest 8 months. All three were male infants.

CASE REPORTS

CASE 1.—P. de F., aged 8 months, was born following a normal pregnancy and an eleven-hour labor. The child was placed in an oxygen tent for the first twenty-four hours of life because of his poor color. The child was taken home at 5 days of age and was said to have had blue fingernails, rapid respirations, and a rapid heart rate at that time. At 5 weeks of age the child was fluoroscoped and x-rayed. The mother was told at that time that her child had an enlarged heart. X-ray therapy to the thymus did not reduce the supracardiac shadow.

The parents were told to prevent the child from crying. As a result the child had been either held or carried eighteen to twenty hours a day. When crying the child became rather dusky, but did not become as blue as he had when he was 5 months of age.

The patient was digitalized at 3 months of age, and he was continued on a maintenance dosage of 5 drops of tincture of digitalis until his death at 8 months of age.

Six days before entry into Children's Hospital, the child was taken to a convalescent home for the purpose of training. While there he was a problem to the nursing staff, and three days after entry he had a "temper tantrum," which did not serve to ameliorate his cardiac condition. Eight to ten hours before entry into The Children's Hospital the patient had a temperature of 102° F. and had five or six clay-colored, watery stools.

The family history was noncontributory.

Physical examination revealed a poorly developed and nourished white male infant 8 months of age. The skin was pale, and there was a marked lack of subcutaneous fat. There was a slight duskiness to the skin. There were scattered râles over both lung fields and a respiratory rate of 28 to 34 per minute. The heart was enlarged to the right and left. The rate was regular and greater than 200 per minute. There were loud heart sounds at the apex with a harsh blowing systolic murmur, which was maximal at the apex. There was also a slapping P. The remainder of the physical examination was negative.

From the Departments of Pediatrics and Pathology, The Children's Hospital, Washington, D. C.

A hemogram on admission showed 16 Gm. of hemoglobin, 6.4 million red blood cells, and 14 thousand white blood cells, with 46 per cent neutrophils and 54 per cent lymphocytes. Urinalysis revealed 100 mg. of albumin, many hyaline casts, rare coarse and fine granular casts, and an occasional white blood cell. The urine specimen was of insufficient quantity for the determination of specific gravity.

The day after entry the temperature rose to 105.4° F., the heart rate was over 200, and there were very rapid, deep respirations. There were eight liquid, greenish yellow stools in twenty four hours. The child was placed in an oxygen tent but expired twelve hours later.

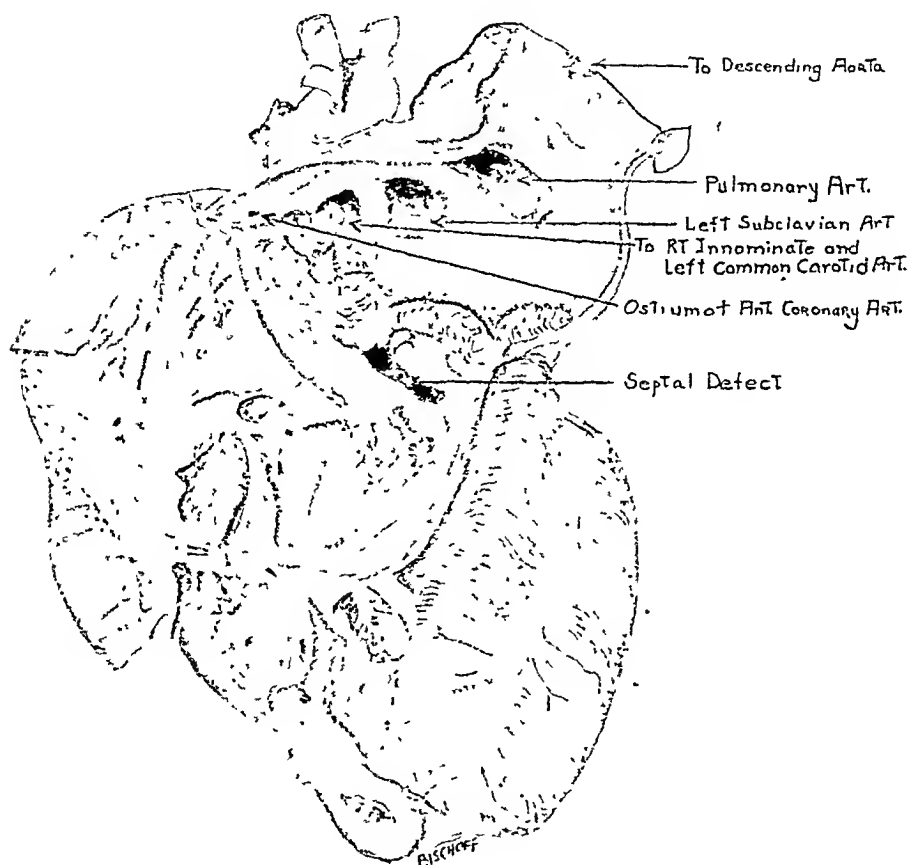


Fig 1—Truncus arteriosus communis

Post-Mortem Findings.—

The body was that of a fairly well developed but poorly nourished white male infant. There was a dearth of subcutaneous fat.

The skull was grossly normal with no unusual prominences or bossing. There was considerable vascular congestion over the convex surface of the brain. The vessels at the base showed no abnormalities. The gyri and sulci appeared to be within normal limits. There was some edema of the meninges. Upon coronal section of the brain, the ventricular system was found to be within normal limits.

The thymus weighed 12 Gm., was pink in color, and soft in consistency. No enlargement was noted of the mediastinal or bronchial lymph nodes; the trachea and bronchi were patent

and grossly normal. The right lung was voluminous, boggy, and contained air. The cut surface was a light red color, and the bronchioles were filled with a pinkish, serous fluid. The left lung was partially collapsed, contained no air, was a dark purple in color, and rubbery in consistency. The cut surface of the left lung was dark purple in color, and no fluid could be expressed from it.

There were approximately 15 c.c. of straw-colored fluid in the pericardial sac. The heart was tremendously enlarged, mostly to the left, and the left lung was compressed by the enlarged heart. After a complete dissection of the heart and great vessels and their secondary branches, it was demonstrated that (1) no ductus arteriosus was present, (2) the aorta gave off only the right innominate and the left common carotid arteries, (3) the pulmonary artery gave rise to the left subelavian artery, and (4) the pulmonary artery, after giving origin to the right and left pulmonary arteries, was continued downward as the descending aorta.

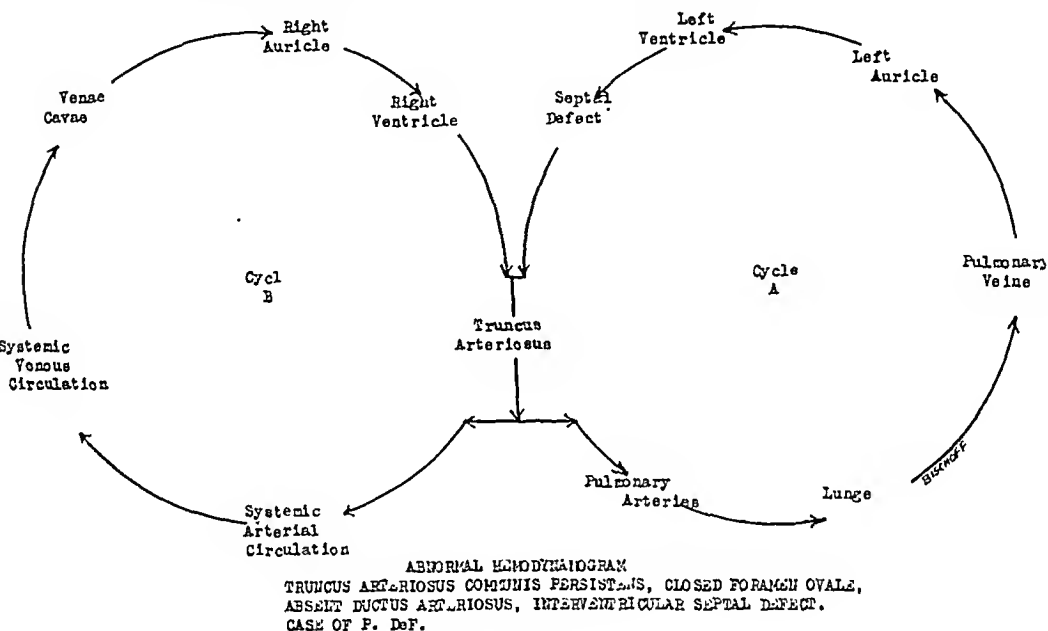


Fig. 2.

Upon opening the heart it was found that the tricuspid and mitral valves each had two leaflets. The leaflets of both valves were thickened along the free edges. There were small ball-like prominences which projected from the superior surface of the free edge of the posterior leaflet of the mitral valve. A large vessel overrode the septum, and the only communication between the left ventricle and this vessel was by way of an interventricular septal defect. This defect was ovoid in shape and measured 12 by 6 mm. in its greatest diameters. What appeared from the outside to be the pulmonary artery was actually a truncus arteriosus communis persistens. This vessel had four cusps, each of which was markedly thickened, fibrous, and red in color. A large vessel, unprotected by valves, was given off from the right side of the truncus so close to its origin that externally it had the appearance of a separate vessel with an individual origin from the base of the heart. This vessel divided into the right innominate and the left common carotid arteries approximately 1.5 cm. distal to its origin. The anterior and posterior coronary arteries originated near the base of the truncus. The truncus, after giving rise to the right and left pulmonary arteries, became the descending aorta. The left subelavian artery was given off from the truncus arteriosus by independent origin.

The remainder of the gross findings were within normal limits.

Microscopic examination of the tissues confirmed the gross impressions and also showed a generalized hemostasis as evidenced by a moderate red cell engorgement of all of the tissues of the thorax and abdomen and of the brain

CASE 2—R M, aged 16 days, first began to have attacks of cyanosis at 6 days of age. These were associated with twitchings of the right side of the face and the right arm. These episodes occurred every two to three days until hospital entry at 16 days of age. The child was said never to have cried unless he was stimulated.

The past history revealed that the child was the product of the mother's third pregnancy. Two other siblings were living and well. The delivery was spontaneous and considered to have been normal.

Physical examination showed the child to be extremely cyanotic and dyspneic. The right side of the face twitched occasionally. The eyes, ears, and nose were normal. The lips were very blue. The lungs were clear to percussion and auscultation. The heart rate was rapid and the rhythm regular. There was a harsh systolic murmur at the third left interspace. The remainder of the physical examination was within normal limits.

The child convulsed continually. The convulsions appeared at more frequent intervals during feeding.

Throughout his hospital stay the child did poorly, and he died thirty hours after admission.

Post Mortem Findings—

At necropsy the lungs showed evidence of edema and congestion, as did the liver, pancreas, kidney, and brain.

The heart was moderately enlarged, weighing 32 Gm as against a normal of 20 Gm. The tricuspid valve measured 3.4 cm in circumference, and the mitral valve, 3.6 cm in circumference. The right ventricular wall averaged 6.5 mm in thickness, and the left ventricular wall averaged 6 mm in thickness. The heart muscle was firm and of normal color. The endocardium showed no changes. The aorta and pulmonary artery were absent, being replaced by a single vessel. The valves of this common trunk had four semilunar cusps and measured 2.4 cm in circumference. No branches were given off by the initial 6 cm of the common trunk. The coronary arteries originated in a position corresponding to their openings in the aortic cone. They appeared slightly enlarged. The interauricular septum consisted of a thin endocardial membrane which was perforated in numerous places. These defects measured from 1.0 to 8 mm in diameter. The pars membranacea of the interventricular septum was defective. This defect measured 3 by 10 mm and was so situated that blood from the left ventricle and right ventricle was injected directly into the common trunk. The ramifications of the common arterial trunk could not be followed since the latter had been severed at a point 6 cm distal to the valve.

CASE 3—C S, aged 2 months, was admitted to The Children's Hospital on Dec 14, 1912. The admission diagnosis was "probable" congenital heart disease. The chief complaint on admission was the appearance of cyanosis and wheezing respirations upon crying.

Physical examination revealed a pale, undernourished white male infant, who became very cyanotic when he began to cry. A marked dyspnea also appeared when the child cried. There was no obvious edema or clubbing. The eyes, ears, nose, and throat were normal. The lungs were considered to be within normal limits. The point of maximal impulse was not definitely visible or palpable, but seemed to be at the left anterior axillary line in the fourth and fifth interspaces. There was a soft systolic murmur best heard along the upper left sternal border (child crying). The rhythm was regular and the rate rapid. Examination of the abdomen was unsatisfactory because of the tense abdominal muscles (crying).

An electrocardiogram showed evidence of right ventricular strain.

X-ray examination of the chest revealed a massive collapse of the left lung with retraction of the heart and great vessels to that side.

Because of the massive collapse, bronchoscopy was performed. The right main bronchus was patent, however the left main bronchus was too narrow to admit the bronchoscope. The suction tip was used as a dilator. As the suction tip passed through the left main bronchus

it gave the sensation of passing over a stricture. A follow-up film after bronchoscopy revealed the entire left lung to have undergone marked aeration.

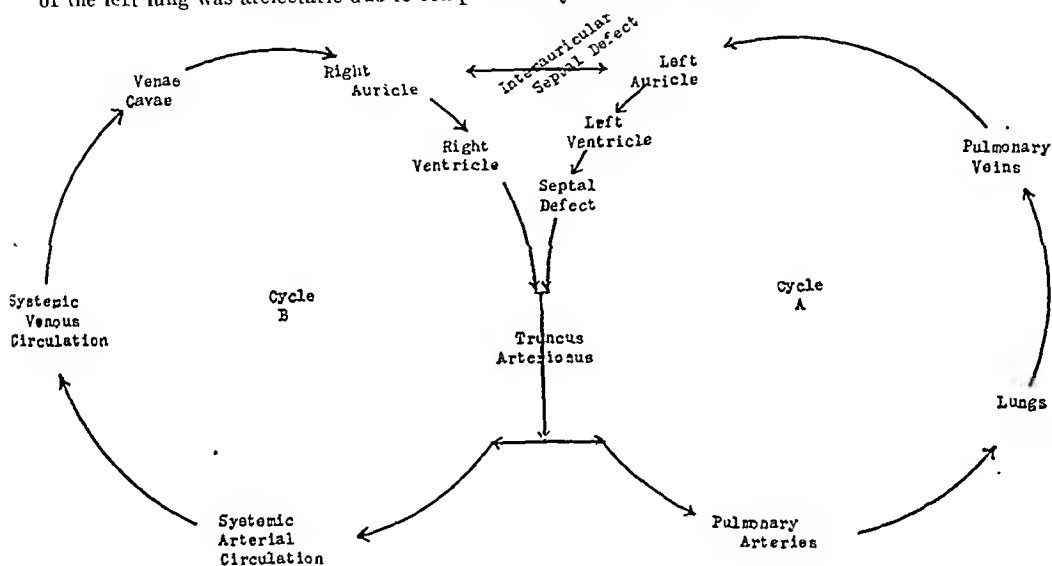
In spite of the apparent alleviation of the pulmonary condition, the child did poorly, became progressively more cyanotic, and expired on Feb. 16, 1942.

Post-Mortem Findings.—

The body was that of an emaciated but normally developed white male infant.

Permission to examine the brain was refused.

The thymus weighed 1.5 Gm. and was atrophic in appearance. No enlargement was noted of the bronchial and mediastinal lymph nodes. The trachea and bronchi were patent and grossly normal. Both lungs showed evidence of a pneumonic process. The middle third of the left lung was atelectatic due to compression by an enlarged heart.



ABNORMAL HEMODYNAMOGRAM
TRUNCUS ARTERIOSUS COMMUNIS PERSISTENS, CLOSED FORAMEN OVALE,
ABSENT DUCTUS ARTERIOSUS, INTERVENTRICULAR SEPTAL DEFECT,
INTERAURICULAR SEPTAL DEFECT. CASES R.M. AND C.S.

Fig. 3.

There were approximately 10 c.c. of clear, pale yellow fluid in the pericardial sac. The heart was rounded in shape and considerably enlarged. It weighed 59 Gm. against a normal of 27 Gm. for an infant 2 months old. Both ventricles were moderately dilated and showed marked hypertrophy of the ventricular musculature. The left ventricular wall averaged 10.5 mm. in thickness, and the right, 13.5 mm. The interventricular septum was defective at the base, the defect measuring 1.3 by 0.7 mm. The mitral valve measured 3.7 cm. in circumference, and the tricuspid valve, 4.1 cm. Those valves were not unusual in appearance except for a moderate thickening of the cusps, which did not appear to be on an inflammatory basis. Both auricles were moderately dilated but not hypertrophied. The interauricular septum showed a defect in its upper portion which measured 0.6 by 0.3 mm. This defect did not correspond to the anatomic position of the foramen ovale.

The aorta and pulmonary artery were replaced at their points of origin and to a length of 2.0 cm. by a common arterial trunk, which sat astride the interventricular defect and apparently received blood from both ventricles. The valve guarding the common trunk measured 3.8 cm. in circumference and possessed three cusps. The cusps were pink in color and larger and more fleshy than those ordinarily seen in the aortic or pulmonary valves. The nodules of Arantius were likewise distinctly larger than normal. The orifices of the right and left coronary arteries were slightly enlarged and were given off from the common trunk.

A vessel, unprotected by valves, was given off at a point 2 cm. above the origin of the common trunk, and this divided into the innominate, left common carotid, and left subclavian arteries. One centimeter beyond the origin of this vessel, the right and left pulmonary arteries were given off. Beyond this point the common truncus arched caudad and continued as the descending aorta.

Microscopic examination:

Lung: The vessels were intensely congested. The alveoli were crowded with leucocytes. Atelectasis was not prominent. One portion of the section showed beginning inflammatory changes; the alveolar spaces contained only a few red cells and polymorphonuclear leucocytes, but their walls were thickened due to leucocytic infiltration.

There was congestion of the remainder of the major visceral organs and granular degeneration of the kidney tubules.

DISCUSSION

It might be considered that with the only avenue of exit for blood from the left ventricle being by way of the interventricular septal defect, the right ventricle might be designated as a common ventricle. However since in all three of these cases the truncus overrode the septal defect, at each systole the blood from the left ventricle must have been forcibly injected into the common trunk with a minimum of mixing in the right ventricle.

In one of these children (Case 1), cyanosis was not a marked feature. This child had only the common trunk with no other complicating anomaly. In Case 2 there were, in addition to the common truncus, multiple perforations of the interauricular septum, which allowed for mixing of oxygenated and unoxygenated bloods prior to their injection into the common trunk. The third child, in addition to the common trunk, also had an interauricular septal defect and a compression of the air passage, which, according to the x-ray findings, undoubtedly interfered with aeration of the blood.

There is included a drawing of the heart (Fig. 1) of Case 1 opened through the right ventricle. This drawing has been labeled to demonstrate the major points.

We have also included two "hemodynamograms,"²² which illustrate the blood circulation in the three cases. The first of these (Fig. 2) shows the circulation as it existed in Case 1. The second (Fig. 3) shows the circulation in Cases 2 and 3 and reveals the effect of introducing a shunt between the two auricles. These pictorial representations give an at-a-glance evaluation of the circulation as it existed during life. It may readily be seen that as the "back pressure" was increased in Cycle A, due to atelectasis, congestion, or edema, more blood was shunted to the systemic circulation. Thus less blood was offered for oxygenation to already poorly functioning organs (the lungs), with resulting anoxia, generalized engorgement of the brain and viscera, right heart failure, and death of the patient.

SUMMARY

1. Three cases of truncus arteriosus communis persistens are presented.
2. Hemodynamograms of the circulation as it existed in life are included, with remarks which speculate on the probable mechanism of death.

We are indebted to Dr. Carl Silverman for his permission to include his patient (Case 3) in this series.

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TRANSFUSIONS IN NEWBORN INFANTS THROUGH ABDOMINAL WALL SEGMENT OF UMBILICAL VEIN

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RECENT medical literature contains several articles dealing with transfusion of the newborn infant via the umbilical vein.^{1,2} The various techniques described have in common the employment of the umbilical vein *within* the umbilical cord. Their applicability is severely limited by the brief period during which the umbilical vein remains patent within the rapidly atrophying cord. Estimates of this period vary between twelve and forty-eight hours. Following is a preliminary report on a method which utilizes that portion of the umbilical vein which lies within the abdominal wall. Here the vein is readily available even after atrophy of the umbilical cord has occurred.

Technique.—A transverse cutaneous incision 2 cm. in length is made 1 cm. cephalad to the upper margin of abdominal insertion of the umbilical cord. Upon separation of the subcutaneous tissue, the umbilical vein is visualized as a whitish, longitudinal, tubular structure elevating the thin midline aponeurosis. A 0.5 cm. longitudinal incision through the aponeurosis is made on either side of the vein, and the latter is easily freed from the underlying transversalis fascia and peritoneum by blunt dissection with tissue forceps and grooved director. After loose application of a fine silk or catgut ligature around the upper exposed portion of the vein, a sharp-pointed scissors is employed to make a transverse nick through its anterior wall. A blunt-tipped nylon cannula, size 18 (or larger, if desirable), is then introduced cephalad until blood can be aspirated through it with ease. The ligature is then tied with a single hitch to effect snug approximation of the vein wall around the indwelling cannula, and transfusion is carried out. Upon termination of transfusion, the cannula is withdrawn, and the ligature is tightened and completed with a second hitch. Skin edges are approximated with two silk sutures.

Anatomical Considerations.—According to Arrey,³ the empty umbilical vessels contract and gradually lose their lumina by fibroblastic proliferation. This process extends through the first two or three months of postnatal life. Scam-

TABLE I. THE UMBILICAL VEIN AND DUCTUS VENOSUS IN THE NEWBORN INFANT (6 CASES)

PATH. NO.	AGE	LENGTH OF U.V. EXTRAPE- RITONEALLY	PATENT U.V.	DIAMETER U.V.	PATENT DUCTUS VENOSUS
32303	9 hr.	3.5 cm.	yes	0.4 cm.	yes
32842	15 hr.	2.5 cm.	yes	0.3 cm.	yes
32970	5 days	4.0 cm.	yes	0.3 cm.	yes
34333	5 hr.	2.5 cm.	yes	0.5 cm.	yes
35497	6 hr.	3.0 cm.	yes	0.4 cm.	yes
35498	3 days	3.0 cm.	yes	0.3 cm.	yes

This work was carried out in the Department of Pathology, the Bronx Hospital, New York, N. Y. Sincere thanks is given to Dr. Joseph Felsen, Director of Laboratories and Research, for his kind guidance and help.

mon and Norris,⁴ in their review of 762 cases, report obliteration of the ductus venosus as follows: in 2.3 per cent the vessel is obliterated within the first week of life; in 18 per cent within the second week; in 37.5 per cent within the third week, and in 100 per cent, it is obliterated after the second month.

Table I is based on findings obtained from postmortem examination of six newborn full-term infants.

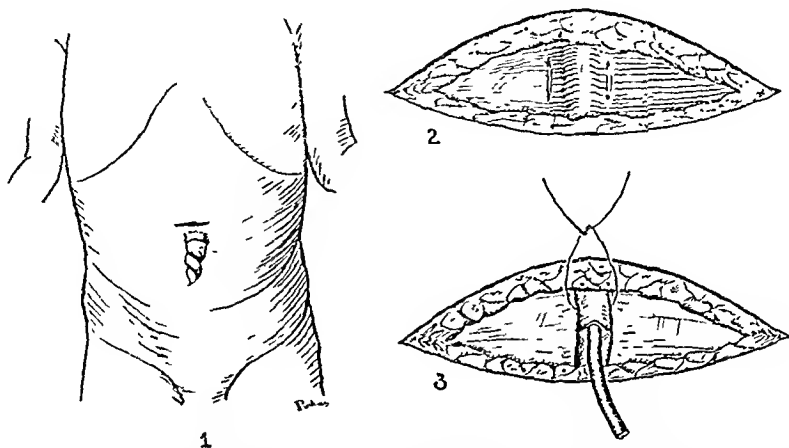


Fig. 1.—Transabdominal wall approach to umbilical vein. 1, Site of incision; 2, close-up of cut-down site after separation of skin and subcutaneous tissue; 3, umbilical vein isolated and cannula being introduced.

It is to be noted from Table I that the umbilical vein was found to be an extraperitoneal structure for a distance of 2.5 to 4.0 cm. cephalad to the upper margin of the umbilicus. Both the umbilical vein and the ductus venosus were patent in each case. The distance from the site of cut-down to the point of junction between the ductus venosus and the inferior vena cava varied between 6 and 8 cm.

Application.—To date, the above-described technique has been employed in transfusing one living newborn infant (Hospital Record No. 201217). The male, erythroblastotic infant, a spontaneous delivery at term, had replacement transfusion therapy instituted twenty-six hours after birth. All attempts at passing a cannula into the umbilical vein via the cord were unsuccessful. Thereupon, the transabdominal wall approach was made. Replacement transfusion, totalling 500 c.c. of blood withdrawn and 540 c.c. infused, was completed with ease.

CONCLUSIONS

A new approach to the umbilical vein is described. The length of time after birth during which this technique is applicable is as yet undetermined but its usefulness far outlasts the approach via the cord. Moreover, the simplicity of technique, the large caliber of the umbilical vein, the toughness

its wall, and its relative isolation from vital structures, render this site most desirable for transfusion techniques in the newborn infant.

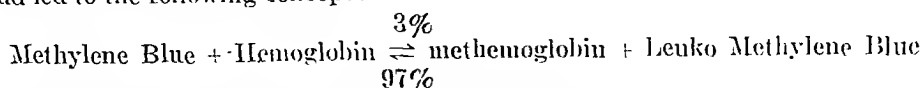
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METHEMOGLOBINEMIA IN YOUNG INFANTS

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CLINICAL interest in cyanosis due to methemoglobinemia increased sharply with the introduction of sulfanilamide therapy and the early demonstration by Wendel¹ and Hartmann, Barnett, and Perley² that methylene blue was a very effective agent in its treatment or prevention. Wendel's work showed that methylene blue caused both formation and disappearance of methemoglobinemia and led to the following concept:



Leuko Methylene Blue + O₂ → Methylene Blue
In vivo, 97 per cent of the reaction was in the direction of methemoglobin → hemoglobin. Methylene blue was also found effective in the treatment of methemoglobinemia resulting from other known agents such as aniline shoe dyes and nitrates, and from unknown or "idiopathic" causes.³ Although sulfanilamide is no longer a widely used drug or a frequent cause of methemoglobinemia, one of the newer sulfonamide derivatives, Promint which is frequently used in conjunction with streptomycin in the treatment of tuberculosis, resembles sulfanilamide in its ability to produce methemoglobinemia and what at times may be confusing cyanosis.

While one of us (A. F. H.) was exploring, with some encouragement but no real success, the possibility that apparently idiopathic methemoglobinemia in the neonatal period might be due to low concentrations of normally occurring reducing substances in the tissues of such young infants, three different investigators, first Comly,⁴ then Faucett and Miller,⁵ and then Ferrant⁶ showed that such infants might really be drinking well water containing nitrate and nitrite and developing cyanosis from such a cause. Recently our own experiences were confirmatory; i.e., instances of apparently "idiopathic" methemoglobinemia were really due to ingestion of well water contaminated with nitrate. There remained, however, the question as to why *only* the *young infants* and not other members of the family developed cyanosis. The following observations we believe answer the question.

EXPERIMENTAL OBSERVATIONS

A. Role of Nitrate.—That the nitrate ion when ingested and converted to nitrite can produce methemoglobinemia is not a new idea. In 1928, Barker and O'Hare⁷ described a case of an adult male who, while receiving 15 Gm. per day

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¹Most of the experimental work reported in this paper was done in competition for the Gill Prize in Pediatrics awarded on graduation from Washington University School of Medicine in June, 1937.

[†]Sodium P,—P'—diaminodiphenylsulfone—N, N' didextrose sulfonate.

of ammonium nitrate, developed cyanosis "presumably because of methemoglobin." Eusterman and Keith⁸ showed that a dosage of 12 Gm. per day of ammonium nitrate for two days produced methemoglobinemia in a 47-year-old woman. Roe⁹ reports two fatal cases of methemoglobinemia in infants given bismuth subnitrate, and for many years it has been pediatric practice to treat diarrhea with bismuth subcarbonate rather than subnitrate to avoid the possibility of nitrite poisoning. Therefore, that the nitrite ion after reduction to nitrite is capable of producing methemoglobin in certain individuals is undoubtedly true.

It was first decided to determine whether the concentration of nitrate-ion fed infants was the important factor in their developing methemoglobinemia. The amount of ingested nitrate per kilogram of body weight per day as noted in the reported cases^{4, 5, 6, 9} and in our own was found to vary from 37.1 mg. to 108.6 mg., with an average of 56.7 mg. per kilogram per day. In nitrite content, the well waters analyzed contained from a trace of 2 mg. per liter, amounts too small to produce methemoglobinemia.

An "artificial well water" was prepared which contained 1 mg. of nitrate ion per cubic centimeter, supplied in the form of sodium nitrate. The solution was autoclaved before incorporation into the infants' formula. Methemoglobin and total hemoglobin levels were determined by the method of Evelyn and Malloy.¹⁰

After feeding 50 mg. of nitrate ion per kilogram per day to four infants ranging in age from 11 days to 11 months for periods of two to eighteen days, the highest level of methemoglobin obtained was 0.75 Gm. per cent (5.3 per cent of the total hemoglobin). No cyanosis was evident. The dosage of nitrate ion was then doubled to 100 mg. per kilogram per day. The increased amount of nitrate was fed to four infants, 2 days to 6 months of age, for periods of six to nine days. The only noteworthy level of methemoglobin, 1.3 Gm. per cent (7.5 per cent of the total hemoglobin) was obtained in an infant 10 days of age eight days after the nitrate solution was added to his formula. Again, no cyanosis was evident.

Then 100 mg. of nitrate ion per kilogram per day were fed to infants who had previously been cyanotic due to the ingestion of well water containing nitrate and in whom treatment with methylene blue had been successful in relieving the cyanosis. The highest level in these babies, who were 6 and 7 weeks of age, was 11 per cent of the total hemoglobin, and this time cyanosis was apparent, but not marked.

Therefore, it appeared that there were other factors in addition to the quantity of nitrate ion ingested that determined whether or not an infant became cyanotic. We decided to investigate first such factors as bacterial well water contaminants and gastrointestinal flora with regard to nitrate reduction and then age, gastric acidity, and the level of intestinal absorption of nitrate.

B. Role of Gastrointestinal and Well Water Bacteria.—In the well waters described in the literature^{4, 5, 6} and in the samples which we analyzed, bacterial contaminants were found. Ours were all of the so-called nonpathogenic varieties

and were chiefly *Acrobacter aerogenes*, aerophylic diplococci, and *Escherichia freundii*. All strains produced nitrite from nitrate.

The saliva, gastric juice, and stools of our cyanotic infants were cultured. Aerophilic streptococci and *A. aerogenes* were found in the saliva and gastric secretions of one infant. In another case, green streptococci, *Staphylococcus aureus*, and *Escherichia coli* were grown from the gastric juice, and a green streptococcus from the saliva. All of these organisms were then grown on simple peptone liquid media, one-half of which contained small amounts of sodium nitrate and one-half of which served as a control and contained no source of nitrate. In twenty-four to forty-eight hours, each tube containing the nitrate and one of the above organisms gave a strongly positive α -naphthalamine sulphonie acid test for nitrite. Therefore, all of the organisms found in the mouths and upper gastrointestinal tracts in two of our cyanotic babies were capable of reducing nitrate to nitrite.

In view of the above findings, some of the contaminated well water was fed to one of the previously cyanotic infants whose methemoglobin level was 0.1 Gm. per cent following therapy. After seventy-two hours, the methemoglobin level rose to 1.4 Gm. per cent or 12.1 per cent of the total hemoglobin, and the infant was cyanotic. Well water, after being sterilized by boiling for fifteen minutes, was fed to a two-month-old infant with meningitis and to another of the treated methemoglobinemia babies. The former's methemoglobin level did not exceed 0.2 Gm. per cent (2 per cent of the total hemoglobin) after sterile well water for two days, at which time the feedings had to be discontinued. The previously cyanotic infant developed methemoglobin levels of 1.26 Gm. per cent (11.1 per cent of the total hemoglobin) after six days and 1.0 Gm. per cent (9.5 per cent) after four days of sterile well-water feedings on two separate occasions. The infant who had been cyanotic continued to have positive gastric juice cultures for *A. aerogenes* and aerophilic streptococci while he was receiving the sterile well water.

In addition, three infants were fed sterilized well water plus interval feedings of a suspension of *A. aerogenes*. Two of the infants were prematures; each developed levels of 8.5 per cent methemoglobinemia in twenty-four hours, at which time the feedings were discontinued because one of the infants developed diarrhea. The third infant fed sterile well water and *A. aerogenes* had a strongly acid gastric juice and did not develop a noteworthy level of methemoglobin despite five days of nitrate feeding.

C. Role of Age and Gastric Acidity.—Examination of the gastric juice of the infants who developed appreciable levels of methemoglobinemia either on well water or nitrate water feedings revealed no free acid to be present and the pII to be greater than 4.0. All of the babies were less than 2 months of age.

In order to determine whether or not the gastric acidity had an effect on the survival of the nitrate reducing bacteria, the organisms which were cultured from the well water, saliva, gastric juice, and stools of one of our cyanotic infants were grown in culture media of various pII. All of the organisms including *A. aerogenes*, *Esch. freundii*, and *Esch. coli* grew in media of pH 5 to pH 7. None grew in media of pH 4.0. These findings are in keeping with

the observations made by Marriott, Hartmann, and Senn¹¹ on infants with diarrhea.

In addition, two of the previously cyanotic babies were placed on formulas containing lactic acid in addition to a source of nitrate. One infant, who had had a methemoglobin level of 0.75 Gm. per cent (7.6 per cent of the total hemoglobin), was placed on a lactic acid-well water formula. The methemoglobin level gradually fell over a period of three days to 0.13 Gm. per cent or 1.3 per cent of the total hemoglobin. The other infant, after attaining a level of 1.3 Gm. per cent of methemoglobin on a formula containing 100 mg. of nitrate ion per kilogram per day, was then treated with methylene blue intravenously and had a methemoglobin level of only 0.1 Gm. per cent after three days of a lactic acid-nitrate water formula.

D. Level of Absorption of Nitrate.—The organisms which we grew from the stools of two of our patients were *Esch. coli* and readily reduced nitrate to nitrite. Since these bacteria are present in almost all lower intestinal tracts, we postulated that the nitrate fed orally to normal babies was absorbed before coming into contact with organisms capable of converting nitrate to nitrite.

Subsequently we had an opportunity to verify this point in a 3-month-old infant in whom a transverse loop colostomy had been done shortly after birth. By injecting 200 mg. of nitrate ion into the colostomy, we obtained a level of methemoglobin of 2.6 Gm. per cent (25 per cent of the total hemoglobin) within four hours; the baby was markedly cyanotic. However, feeding the infant 600 mg. of nitrate ion daily for two days resulted in a methemoglobin level of only 0.5 Gm. per cent or $\frac{1}{4}$ per cent of the total hemoglobin. Apparently most of the ingested nitrate had been absorbed before reaching the colon where the bacterial conversion to nitrite took place in this case.

DISCUSSION

From the foregoing observations we feel that only the young infants and not the older members of the family develop methemoglobinemia following the ingestion of well water containing nitrate, because of several factors. In young infants, nitrite-producing organisms can exist high in the gastrointestinal tract in sufficient numbers to reduce nitrate to nitrite before the former can be completely absorbed. This is because of the characteristic low acidity of the gastric juice in the neonatal period. It seems to us unlikely that the adult members of the family fail to develop methemoglobinemia merely because they ingest relatively less contaminated well water. In our group of control infants with good gastric acidity, very large amounts of nitrate were fed without the production of cyanosis or significant amounts of methemoglobinemia.

Many organisms, both pathogenic and nonpathogenic, are capable of converting nitrate to nitrite. No special significance need be attributed to the particular "nonpathogenic" contaminants grown from the well water other than that they were able to survive in the stomach and upper small intestine. However, we would predict that infants, in whom *Esch. coli* were permitted to infest heavily the stomach and duodenum by migrating from the lower intestinal tract

in the presence of a low gastric acidity, would also develop methemoglobinemia if fed nitrate water. Such a situation would simply be analogous to that described when nitrate was introduced into the transverse colon.

If severe cyanosis is present, treatment of choice is intravenous methylene blue, 1.0 to 2.0 mg. per kilogram.^{1, 2} In prevention, while it is true that lactic acid added to the formula in the usual amounts (final concentrations 0.5 to 1 per cent) prevented the formation of methemoglobinemia, it seems safer to prohibit ingestion of nitrate water until infants are old enough to develop good gastric acidity.

SUMMARY AND CONCLUSIONS

1. The problem of methemoglobinemia in infancy following the ingestion of nitrate was studied.
2. Only infants who have a gastric juice pH higher than 4.0 and nitrate-reducing bacteria in the upper gastrointestinal tract develop methemoglobinemia from oral ingestion of water containing nitrate.
3. It was demonstrated that if nitrate is introduced into the colon, methemoglobinemia develops readily.
4. The treatment of choice for the cyanosis is intravenous administration of methylene blue, 1.0 to 2.0 mg. per kilogram.
5. The prevention of methemoglobinemia can be accomplished by adding lactic acid to the nitrate containing formula to inhibit bacterial growth in the upper gastrointestinal tract as well as by prohibiting the ingestion of nitrate.

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THE SIGNIFICANCE OF POSITIVE BLOOD CULTURES IN NEWBORN INFANTS

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IT IS not uncommon nursery experience to observe certain newborn infants who regularly lose weight beyond the usual expected time and who exhibit a lack of interest in nursing regardless of type of feeding. More often than not careful examination reveals no very convincing reason for the anorexia, listlessness, and accompanying weight loss. If allowed to go unchecked, loss of weight may be very considerable, and energetic and supportive treatment becomes imperative. The writers observed a suggested relationship between this clinical picture and blood cultures which were quite regularly positive for hemolytic staphylococci. In August, 1946, a study was begun for the purpose of clarifying this clinical impression.

This report is concerned with 323 blood culture samples taken from 240 infants, some of whom presented with surprising regularity the above clinical picture. In others the nursery course was uneventful. The number of blood cultures and the number of infants included in this study would seem to be significant.

In a partial review of the literature we find scant reference to bacteremia in the newborn infant. Older references to sepsis of the newborn infant are in most instances confusing and lacking in adequate blood studies. Usually these older reports described a severe type of illness, with death the usual rule, characterized by fever, severe gastrointestinal disturbance, jaundice, hemorrhage, and serious lesions noted at autopsy in the various body systems. The most informative study and the one most regularly referred to is that of Dunham.¹ She reported the findings in thirty-nine cases of septicemia of the newborn infant collected from the records of the New Haven Hospital and occurring over a period of five years. In thirty-four of her cases the diagnosis was made from blood cultures taken before death. She further recorded the findings in 115 blood cultures taken at random from forty-nine apparently healthy newborn infants. *Staphylococcus albus* was recovered in thirty-five instances from these apparently well infants. Dunham concluded that *Staph. albus*, since it could regularly be cultured from the skin of newborn infants, should not be considered as a cause of illness but rather as a skin contaminant when present in blood cultures in the neonatal period. This conclusion has been generally accepted as a fact.

The data recorded in this study suggest that hemolytic *Staph. albus* is capable of invading the blood stream of newborn infants with surprising regularity, and, if present in sufficient numbers, may cause regular and marked weight loss and at times serious signs of illness.

All bacteriologic studies were done under the direction of Dr. William E. Bray, director of clinical laboratories at the University of Virginia Hospital. The helpful cooperation of this department, so essential to this investigation, is gratefully acknowledged.

The procedure employed in obtaining blood samples was as follows: The skin was cleansed with iodine and alcohol. Blood was obtained from the internal jugular vein. In a few instances the femoral vein was used. Blood samples were placed in dextrose carbonate hormone media and in blood agar at forty-eight hours and ninety-six hours. Throughout most of the study subcultures were made on Löffler's medium and plain agar. Toward the end of the study subcultures were made in dextrose lactose and mannite media.

Table I describes the relative frequency of blood cultures positive for hemolytic staphylococci in thirty-four infants from whom blood samples were taken for cause. In every instance the cause was progressive loss of weight frequently associated with anorexia, lassitude, or irritability, for which signs of illness no obvious reason was apparent. All thirty-four infants were observed toward the end of this study and the identity of the organisms seemed clearly established.

Hemolytic *Staph. albus* was identified from culture in twenty-one instances; nonhemolytic *Staph. albus* was cultured in three instances; hemolytic *Staphylococcus aureus* in four instances; nonhemolytic *Staph. aureus* in one instance. Other organisms recovered and considered as contaminants were diphtheroids in one instance, *Bacillus subtilis* in one instance. First cultures were taken at from seven to sixteen days of age, the average age for first culture being ten days. First cultures were positive for hemolytic staphylococci, usually of the *albus* variety, in 64.7 per cent of this series. Granted that *Staph. albus* is a very common contaminant of blood cultures, it is difficult to suppose that contamination from the skin would occur with such frequency and regularity.

As a control series blood culture samples were taken at random from fifty newborn infants. No infant was considered eligible for this control series whose progress in the nursery was unsatisfactory, or who showed any signs of illness. Blood samples were taken at different seasons of the year. The identity of the organisms recovered from positive cultures seemed clearly established. Hemolytic *Staph. albus* was identified in thirteen instances; nonhemolytic *Staph. albus* in three instances; hemolytic *Staph. aureus* in four instances. Other organisms recovered and considered as contaminants were diphtheroids in one instance, hay bacillus in one instance.

As a second control series it seems permissible to include blood samples from fifty-six additional newborn infants. These infants were observed early in the study when one technician had difficulty in distinguishing between *Staph. albus* and *Staph. aureus*. For this reason the staphylococci recovered in cultures will be referred to as hemolytic and nonhemolytic staphylococci. In thirty positive cultures hemolytic staphylococci were identified in twenty-one instances, nonhemolytic staphylococci in one instance. Other organisms recovered and considered as contaminants were *Bacillus aerogenes* (1), coliform bacillus (1) beta

TABLE I

NO.	HISTORY NUMBER	NURSERY	FIRST CULTURE			SECOND CULTURE			THIRD CULTURE			FOURTH CULTURE		
			DATE	AGE IN DAYS	RESULT	DATE	RESULT		DATE	RESULT		DATE	RESULT	
1	237437	WCN	26 March	47	12	<i>Staph. albus</i> , hemolytic	10 April	47	Negative					
2	238173	PCN	17 April	17	16	<i>Staph. albus</i> , hemolytic								
3	238219	PCN	17 April	17	14	<i>Staph. albus</i> , hemolytic; micrococci								
4	238280	WCN	13 April	47	9	Negative								
5	238507	WCN	16 April	47	7	<i>Staph. albus</i> , hemolytic								
6	238758	WCN	26 April	47	11	Negative								
7	238823	WCN	26 April	47	9	Negative								
8	238843	WCN	29 April	47	11	<i>Staph. albus</i> , hemolytic	3 May	47	<i>Staph. aureus</i> , hemolytic	9 May	47	Negative		
9	239553	WCN	18 May	47	10	<i>Staph. albus</i> , nonhemolytic								
10	239559	WCN	18 May	47	10	<i>Staph. albus</i> , hemolytic	22 May	47	Negative					
11	240235	WCN	5 June	47	10	<i>Staph. albus</i> , hemolytic	11 June	47	Negative					
12	240297	WCN	7 June	47	11	<i>Staph. aureus</i> , hemolytic	11 June	47	Negative					
13	240329	WCN	5 June	47	8	Negative								
14	240387	WCN	7 June	47	9	<i>Staph. albus</i> , hemolytic	11 June	47	Negative					
15	240388	WCN	8 June	47	10	Negative								
16	240529	WCN	12 June	47	9	<i>Staph. albus</i> , hemolytic	17 June	47	Negative					

		17	210991	WCN	25 June	47	11	<i>Staph. albus</i> , hemolytic; <i>Staph. aureus</i> , hemolytic and nonhemolytic	30 June	47	<i>Staph. aureus</i> , nonhemolytic	6 July	47	<i>Staph. albus</i> , hemolytic	11 July	47	Negative
18	241051	WCN	25 June	47	10	Negative											
19	241328	WCN	3 July	47	9	Diphtheroids											
20	241511	WCN	9 July	47	11	<i>Staph. albus</i> , hemolytic			12 July	47	<i>Bacillus</i> <i>subtilis</i>	6 Aug.	47	Negative			
21	242108	WCN	22 July	47	9	<i>Staph. albus</i> , hemolytic			29 July	47	<i>Staph. albus</i> , <i>Staph. aureus</i> , hemolytic;	4 Aug.	47	Negative			
22	243080	CCN	13 Aug.	47	9	<i>Staph. albus</i> , hemolytic			18 Aug.	47	hemolytic <i>Staph. albus</i> , hemolytic	20 Aug.	47	<i>Staph. albus</i> hemolytic			
23	245171	WCN	6 Oct.	47	10	<i>Staph. albus</i> , hemolytic											
24	245734	WCN	23 Oct.	47	11	hemolytic			31 Oct.	47	<i>Staph. albus</i> , hemolytic						
25	245813	WCN	26 Oct.	47	13	<i>Staph. albus</i> , hemolytic			2 Nov.	47							
26	245917	PCN	24 Oct.	47	7	<i>Staph. albus</i> , hemolytic			3 Nov.	47	Negative						
27	246223	WCN	11 Nov.	47	7	Negative											
28	246994	WCN	22 Nov.	47	9	Negative											
29	247187	PCN	8 Dec.	47	10	Diphtheroids											
30	247635	WCN	14 Dec.	47	12	<i>Staph. albus</i> , hemolytic			19 Dec.	47	<i>Staph. albus</i> , hemolytic						
31	247762	WCN	13 Dec.	47	8	<i>Staph. aureus</i> , hemolytic			18 Dec.	47	<i>Staph. albus</i> , hemolytic	23 Dec.	47	Negative	26 Dec.	47	<i>Staph. albus</i> , nonhemolytic
32	247874	WCN	19 Dec.	47	11	Negative											
33	248920	WCN	30 Dec.	47	9	Negative											
34	249080	WCN	20 Jan.	48	9	<i>Staph. albus</i> , hemolytic											

WCN, White Children's Nursery.

PCN, Premature Children's Nursery.

CCN, Colored Children's Nursery.

TABLE 11

No.	HISTORY NUMBER	NURS- ERY	FIRST CULTURE			SECOND CULTURE			THIRD CULTURE			FOURTH CULTURE		
			DATE	AGE IN DAYS	RESULT	DATE	RESULT	DATE	RESULT	DATE	RESULT	DATE	RESULT	DATE
1*	210707	PCN	30 Aug.	15	Hemolytic staphylococcus	31 Aug.	45 Negative	3 Sept.	45 Hemolytic staphylo- coccus	3 Sept.	45 Hemolytic staphylo- coccus	3 Sept.	45 Hemolytic staphylo- coccus	3 Sept.
2*	218099	WCN	5 Oct.	15	Hemolytic staphylococcus	7 Oct.	45 Negative	7 Oct.	45 Negative	7 Oct.	45 Negative	10 Oct.	45 Hemolytic staphylo- coccus	10 Oct.
3	218209	WCN	7 Oct.	15	Diphtheroids	13 Oct.	45 Hemolytic staphylococcus	15 Oct.	45 Hemolytic staphylo- coccus	15 Oct.	45 Hemolytic staphylo- coccus	25 Oct.	45 Negative	25 Oct.
4	218361	WCN	13 Oct.	45	Hemolytic staphylococcus	18 Oct.	45 Hemolytic staphylococcus	25 Oct.	45 Negative	25 Oct.	45 Negative	25 Oct.	45 Negative	25 Oct.
5*	219816	WCN	23 Nov.	45	Hemolytic staphylococcus	27 Nov.	45 <i>Str. fecalis</i> ; hemolytic	1 Dec.	45 Negative	1 Dec.	45 Hemolytic staphylo- coccus	1 Dec.	45 Hemolytic staphylo- coccus	1 Dec.
6	220018	WCN	18 Dec.	45	Hemolytic staphylococcus	20 Dec.	45 Hemolytic staphylococcus	28 Dec.	45 Negative	28 Dec.	45 Negative	3 June	46 Negative	3 June
7	220034	WCN	25 May	46	Hemolytic staphylococcus	27 May	46 Hemolytic staphylococcus	1 June	46 Hemolytic staphylo- coccus	1 June	46 Hemolytic staphylo- coccus	3 June	46 Negative	3 June
8	226120	WCN	31 May	46	Hemolytic staphylococcus	3 June	46 Hemolytic staphylococcus	7 June	46 Hemolytic staphylo- coccus	7 June	46 Hemolytic staphylo- coccus	22 June	46 Diphtheroids	22 June
9*	226514	WCN	8 June	46	Nonhemolytic staphylococcus	12 June	46 Nonhemolytic staphylococcus	15 June	46 Negative	15 June	46 Negative	12 Sept.	46 Diphtheroids	12 Sept.
10	226517	WCN	26 Aug.	16	Negative	27 Aug.	46 Nonhemolytic staphylococcus	5 Sept.	46 Hemolytic staphylo- coccus	5 Sept.	46 Hemolytic staphylo- coccus	4 Sept.	46 Flavobac- terium	4 Sept.
11	226562	WCN	25 Aug.	16	Hemolytic staphylococcus	27 Aug.	46 Hemolytic staphylococcus	1 Sept.	46 Hemolytic staphylo- coccus	1 Sept.	46 Hemolytic staphylo- coccus	4 Sept.	46 Flavobac- terium	4 Sept.
12	230226	PCN	24 Sept.	46	Nonhemolytic staphylococcus	29 Sept.	46 Hemolytic staphylococcus	4 Oct.	46 Negative	4 Oct.	46 Negative			

No.	Cult.	PCN	FIFTH CULTURE			SIXTH CULTURE			SEVENTH CULTURE		
			14 Sept.	16	9 Negative	15 Sept.	46 Hemolytic staphylococcus	24 Sept.	46 Diptheroids	29 Sept.	46 Beta hemolytic staphylococcus
13*	230228	PCN									
14	230783	WCN	24 Sept.	46	6 Hemolytic staphylococcus	27 Sept.	46 Hemolytic staphylococcus	29 Sept.	46 Negative	7 Oct.	46 Negative
15	232293	WCN	8 Nov.	46	10 Nonhemolytic staphylococcus	10 Nov.	46 Nonhemolytic staphylococcus	16 Nov.	46 Hemolytic staphylococcus		
16	235349	PCN	28 Jan.	47	11 Hemolytic staphylococcus	2 Feb.	47 <i>B. coli</i>	6 Feb.	47 Nonhemolytic staphylococcus	9 Feb.	47 Negative
17	238843	WCN	29 April	47	11 Hemolytic staphylococcus	3 May	47 Hemolytic staphylococcus	9 May	47 Negative		
18	240994	WCN	25 June	47	11 Hemolytic and nonhemolytic staphylococcus	30 June	47 Nonhemolytic staphylococcus	6 July	47 Hemolytic staphylococcus	11 July	47 Negative
19	242108	WCN	22 July	47	9 Hemolytic staphylococcus	28 July	47 Hemolytic staphylococcus	4 Aug.	47 Negative		
20	243030	CCN	13 Aug.	47	9 Hemolytic staphylococcus	18 Aug.	47 Hemolytic staphylococcus	20 Aug.	47 Hemolytic staphylococcus		
21	245734	WCN	23 Oct.	47	11 Hemolytic staphylococcus	31 Oct.	47 Hemolytic staphylococcus				
22	247635	WCN	4 Dec.	47	12 Hemolytic staphylococcus	19 Dec.	47 Hemolytic staphylococcus				
23	247762	WCN	13 Dec.	47	8 Hemolytic staphylococcus	18 Dec.	47 Hemolytic staphylococcus	23 Dec.	47 Negative	26 Dec.	47 Nonhemolytic staphylococcus
1			10 Sept.	45	<i>B. proteus</i>	12 Sept.	45 Negative	21 Sept.	45 Negative		
2			21 Oct.	45	Negative						
3			12 Dec.	45	Hemolytic						
9			26 June	46	staphylococcus						
13			3 Oct.	46	Negative						

hemolytic streptococcus (1) diphtheroids (2) and micrococci (1). The percentage of cultures positive for staphylococci in the combined control series was 39.56 per cent.

Table II describes the regularity with which repeat cultures positive for hemolytic staphylococci were obtained in twenty-three infants from which blood samples were taken for cause and found to be positive for hemolytic staphylococci.

Repeat cultures were positive for staphylococci in every instance, or 100 per cent. It would seem unreasonable to believe that staphylococci present in the skin surface could contaminate blood cultures with this regularity even if no cleansing of the skin surface had been practiced. The frequency with which repeat positive cultures were obtained compares favorably with repeat positive cultures in bacteremia in other age groups and of more familiar etiology.

From Jan. 2, 1947, to Jan. 31, 1947, 200 blood cultures were drawn at the University of Virginia Hospital on all services. The findings in these two hundred consecutive blood cultures were as indicated in Table III.

TABLE III

<i>Adults: total cultures, 148; positive, 25; negative, 123.</i>					
	Hemolytic staphylococci				6
	Nonhemolytic staphylococci				5
	Diphtheroids				7
	Micrococci				4
	Yeastlike organisms				1
	Mold				2
	Total				25
<i>Children: total cultures, 11; positive, 2; negative, 9.</i>					
	Hemolytic staphylococci				1
	Mold				1
	Total				2
<i>Newborn infants: total cultures, 41; positive, 22; negative, 19.</i>					
	Hemolytic staphylococci				14
	Hemolytic staphylococci and Beta hemolytic streptococci				1
	Nonhemolytic staphylococci and micrococci				1
	Diphtheroids				2
	Micrococci				2
	Coliform bacilli				1
	Bacillus pyocyaneus				1
	Total				22
	TOTAL CULTURES	TOTAL POSITIVE	POSITIVE FOR STAPH.	PER CENT POSITIVE	PER CENT POSITIVE FOR STAPH.
Adults	148	25	11	16.88	7.44
Children	11	2	1	18.18	9.09
Newborn infants	41	22	16	53.65	39.02
Total	200	49	28	24.50	14.00

For the purpose of further investigating the probability of contamination from the skin, the following observations were made with forty newborn infants as subjects. The skin of the lateral side of the neck was prepared with iodine and alcohol in the usual fashion: 5 c.c. of reconstituted dried plasma were drawn into a syringe, both syringe and needle having previously been autoclaved; 2.5 c.c. of the plasma were placed in beef broth and cultured, thus serving as con-

trols. The 2.5 c.c. of plasma remaining in each syringe were injected under the skin in the posterior triangle of the neck behind the posterior border of the belly of the sternomastoid muscle at the juncture of the lower and middle thirds of the muscle. The needle was inserted in the same direction and manner as was regularly done in obtaining blood samples for culture. Plasma was injected and aspirated back and forth several times and was placed in separate flasks of broth for culture. In the final aspiration at least 1.5 c.c. of injected plasma were recovered. This would seem an ample amount to insure thorough rinsing of the lumen of the needle. In one instance both control and injected cultures were positive for *Staph. albus*. We assume that the syringe was contaminated in this one instance and these two cultures were discarded. In the remaining thirty-nine instances the control cultures showed no growth. Of the thirty-nine culture flasks containing samples of injected plasma, ten showed bacterial growth. The organisms were identified as hemolytic *Staph. albus* in eight instances, colon bacillus in one instance, and hemolytic *Staph. aureus*, coagulase positive, in one instance.

As a control study the above procedure was repeated in twenty older infants and runabout children. Samples of injected plasma and controls were negative with one exception. In one instance only a sample of injected plasma was positive for hemolytic *Staph. aureus*.

It would seem to be clearly established that the bacterial flora of the skin of newborn infants is unusually rich in members of the staphylococcus group as compared with the skin of other age groups.

It is a routine nursery procedure in our hospital to apply penicillin ointment once a day to the skins of all newborn infants. This procedure has proved very effective in the prevention of impetigo neonatorum. No studies have been made to determine the possible effect of this daily procedure on the instance of positive blood culture.

If hemolytic *Staph. albus* invades the blood stream of newborn infants with and without symptoms as suggested in this study, it would seem not unlikely that such bacteremia might be prevented.

Preventive therapy was attempted in three separate series of infants. The plan of study was as follows: Beginning at 24 hours of age, every other full-term infant admitted to our nursery was given 5,000 units of penicillin every three hours for a period of four days. Twenty-four hours after the last dose of penicillin a blood sample was drawn. Those infants not receiving penicillin were used as controls.

Series I consisted of eighteen treated infants and eighteen controls. Series II consisted of twenty-five treated infants and twenty-four controls. Series III consisted of twenty-four treated infants and twenty-five controls. From the sixty-seven treated patients twenty cultures positive for staphylococci were obtained. From the sixty-seven controls twenty cultures positive for staphylococci were obtained. Penicillin therapy started at the end of twenty-four hours and administered in the above doses was not effective in the prevention of cultures positive for staphylococci. Perhaps better results might be expected if prevention treatment were delayed until the fourth or fifth day. The rapid

turnover in our nurseries during the past year has prevented further study along these lines.

TREATMENT

Penicillin has been regularly used in the treatment of the clinical picture described in this report. In some instances the addition of sulfadiazine has appeared to speed recovery. Ten thousand units of penicillin intramuscularly every three hours is the dosage presently used. With this dosage, prompt and regular weight gains have been the rule with corresponding improvement in the infant's general condition. Early diagnosis and prompt therapy have markedly reduced the necessity for parental infusions and blood transfusions.

Figs. 1 to 8 present graphically the nursery course in regard to weight curve type of therapy and response to therapy in typical examples.

Additional case protocols are included which describe response to therapy and the frequency of repeat positive cultures.

CASE NO. 240297 MAY 1947

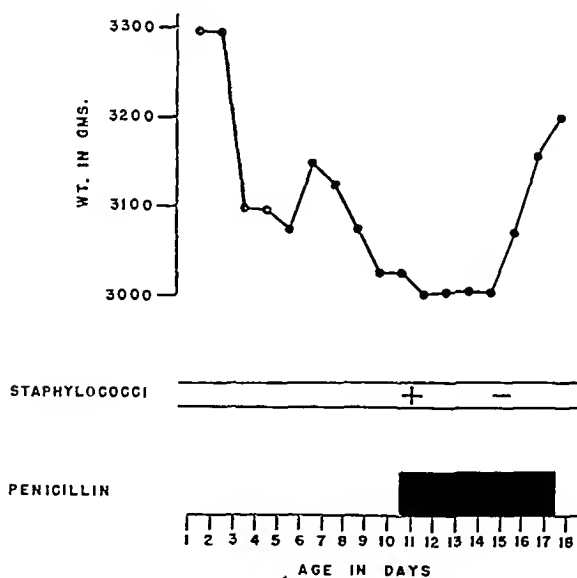


Fig. 1.

CASE PROTOCOLS

CASE 217163.—A white female infant was born Aug. 29, 1945, weighing 2,890 Gm. Delivery followed a normal pregnancy and labor. The nursery course was uncomplicated until the ninth day when the infant began to lose weight. Four days later she began vomiting and developed a watery diarrhea. This was treated in the usual manner, and subsided by the twenty-second day. However, the patient still failed to gain weight and ran an elevation of temperature from the twenty-fourth to the thirtieth day. A blood culture drawn on the thirty-second day was reported as positive for hemolytic staphylococci. A blood culture

repeated two days later was again positive for hemolytic staphylococci. The infant was treated with penicillin 5,000 units q3h and sulfadiazine .065 Gm. five times daily. With this therapy a satisfactory weight curve was established. After two negative blood cultures were obtained the child was discharged in good condition on the fifty-ninth hospital day. No follow-up was available.

CASE NO. 247762 DEC. 1947

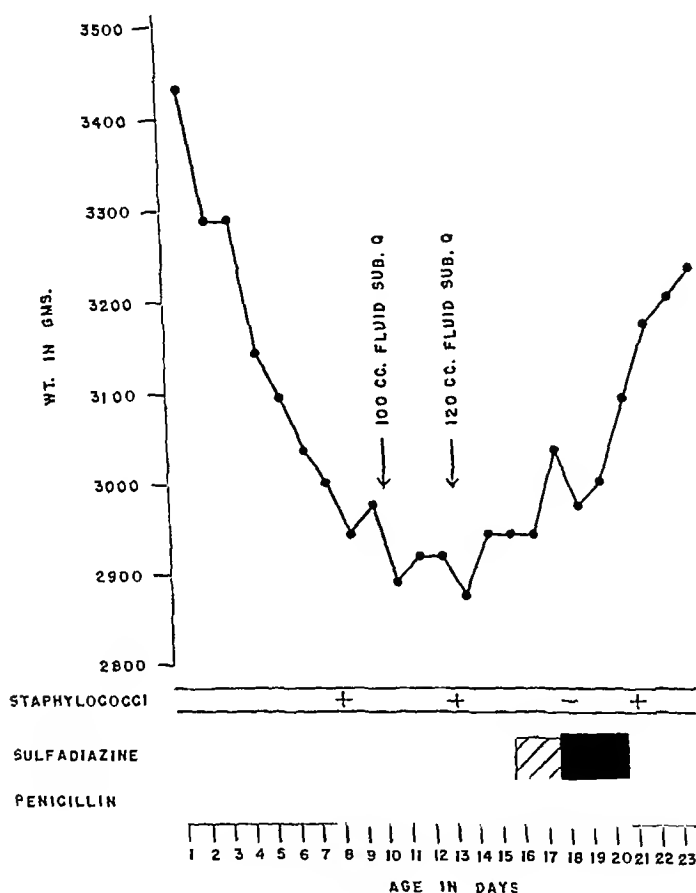


Fig. 2.

CASE 218209.—A white male infant was born Sept. 28, 1945, weighing 3,775 Gm. Delivery followed a normal pregnancy and labor. This infant was apparently well and had a good appetite, but failed to make satisfactory weight gain. A blood culture obtained on the tenth day was reported positive for diphtheroids. A repeat culture on the sixteenth day was reported as positive for hemolytic staphylococci. Two blood cultures were obtained on the eighteenth day and sent to separate laboratories. They were both reported as positive for hemolytic staphylococci. Penicillin 5,000 units q3h, sulfadiazine .065 Gm. six times daily were administered with a satisfactory weight gain being established promptly. He was discharged on the thirty-second day in good condition following a negative blood culture. He was seen three weeks after discharge and was in good condition.

CASE NO. 218361 OCT. 1945

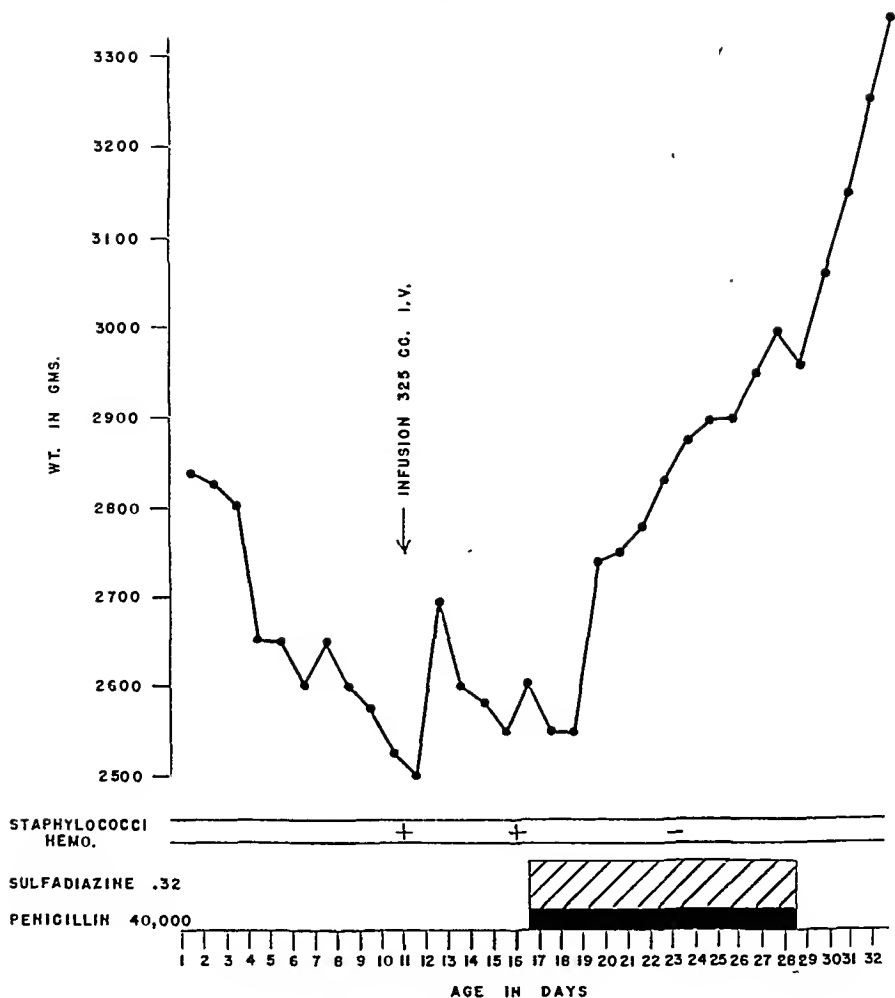


Fig. 3.

CASE 218361.—A white male infant was born Oct. 3, 1945, weighing 2,835 Gm. Delivery followed a normal pregnancy and labor. The nursery course was complicated by anorexia and failure to gain weight. There were no temperature elevations and physical examination was negative. Blood culture drawn on the eleventh day was reported positive for hemolytic staphylococci. A repeat blood culture on the sixteenth day was again positive for this organism. Penicillin 5,000 units and sulfadiazine .065 Gm. five times daily were started on the seventeenth day. The infant's appetite improved immediately and he began making daily weight gains. He was discharged on the thirty-second day in good condition following a negative blood culture. No follow up was available. (See Fig. 3.)

CASE 218809.—A white female infant was born Oct. 17, 1945, weighing 3,675 Gm. Delivery followed a normal pregnancy and labor. The nursery course was complicated by anorexia and a steady weight loss. A blood culture drawn on the eleventh day was reported as positive for hemolytic staphylococci. A repeat blood culture on the thirteenth day was

CASE NO. 220648 DEC. 1945

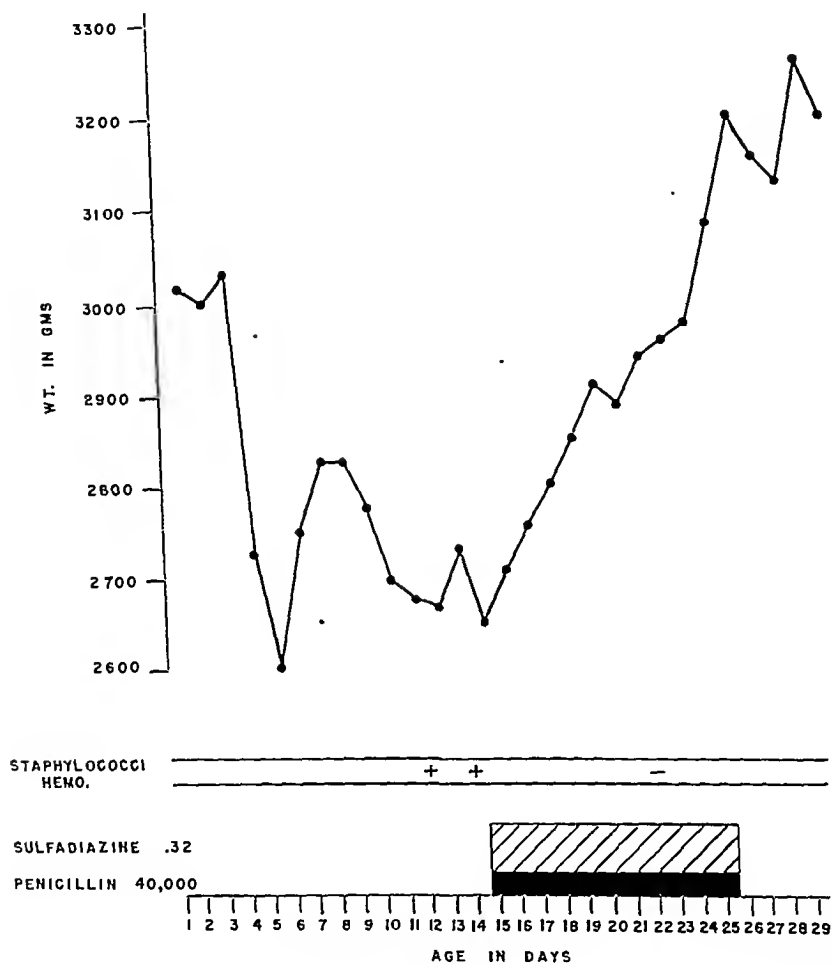


Fig. 4.

lost. On the thirteenth day the patient was started on penicillin 5,000 units q3h. A satisfactory weight curve was established. He was discharged on the twenty-second day in good condition following a negative blood culture. No follow-up was available.

CASE 220648.—A white male infant was born Dec. 7, 1945, weighing 3,015 Gm. Delivery followed a normal pregnancy and labor. The nursery course was complicated by anorexia and a steady weight loss. At no time was there an elevation of temperature and the physical examination was negative. A blood culture drawn on the twelfth day was reported positive for hemolytic staphylococci. A repeat blood culture on the fourteenth day was positive for the same organism. Penicillin 5,000 units q3h and sulfadiazine .065 Gm. five times daily were started on the fifteenth day. There was an immediate improvement in appetite and a satisfactory weight gain was established. The infant was discharged in good condition on the twenty-ninth hospital day following a negative blood culture. No follow-up was available. (See Fig. 4.)

CASE 219846.—A white male infant was born Nov. 10, 1945, weighing 3,600 Gm. Delivery followed a normal pregnancy and labor. The nursery course was complicated by anorexia and inconsistent weight gain. Sulfadiazine .065 Gm. five times daily was started. A blood culture drawn on the eleventh day was reported as positive for penicillin resistant strain of hemolytic staphylococci. Penicillin 10,000 q3h intramuscularly was given in addition to the sulfadiazine. A blood culture drawn on the fifteenth day was positive for hemolytic staphylococci, again penicillin resistant, and *Streptococcus fecalis*. The infant's appetite picked up and he gained weight consistently. Blood culture on the eighteenth day was negative. Therapy was discontinued on the twenty-fourth day. A blood culture was drawn on the twenty-eighth day and he was discharged on that day in good condition. This last blood culture was reported as positive for hemolytic staphylococci.

CASE NO. 226034 MAY 1946

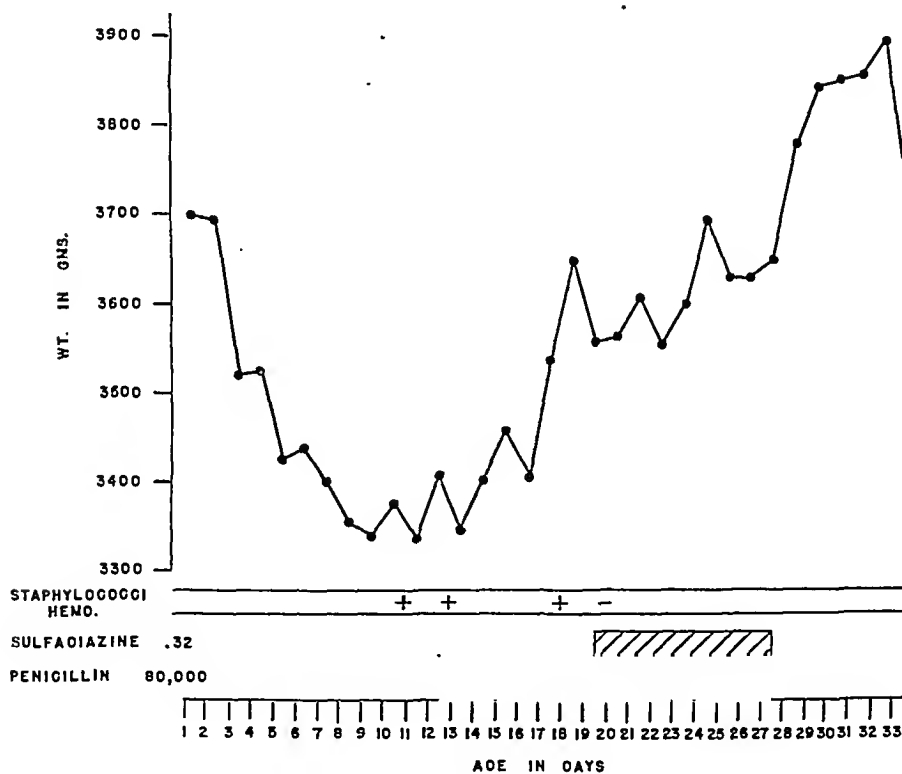


Fig. 5.

CASE 230783.—A white male infant was born Sept. 19, 1946, weighing 3,310 Gm. Labor was complicated by slight premature separation of placenta near term. Weight gains were unsatisfactory and a blood culture drawn on the sixth hospital day was positive for hemolytic staphylococci. A second blood culture drawn on the ninth hospital day was again positive for hemolytic staphylococci. Penicillin 10,000 units q3h was started on the tenth hospital day. A blood culture drawn on the eleventh hospital day was negative; however, weight gains were not satisfactory until the sixteenth hospital day. A final blood culture drawn on the nineteenth hospital day was negative and the infant was discharged on the twenty-first day after six days of progressive weight gain. The child has been followed in the clinic and is a healthy infant.

CASE 226034.—A white female infant was born May 15, 1946, weighing 3,700 Gm. The mother had active tuberculosis and a low cervical cesarean section was performed. There were only three weight gains in the first eleven days. A blood culture drawn on the eleventh day was reported as positive for hemolytic staphylococci. Penicillin 10,000 units q3h were started on the thirteenth hospital day. Following this therapy weight gains were satisfactory. Blood cultures drawn on the thirteenth and seventeenth hospital days were again reported as positive for hemolytic staphylococci. Sulfadiazine .065 Gm. q4h five times daily was started on the nineteenth hospital day. A blood culture drawn on the twentieth hospital day was reported as negative. The infant was discharged on the thirty-second hospital day. No follow-up was available. (See Fig. 5.)

CASE NO. 229562 AUG. 1946

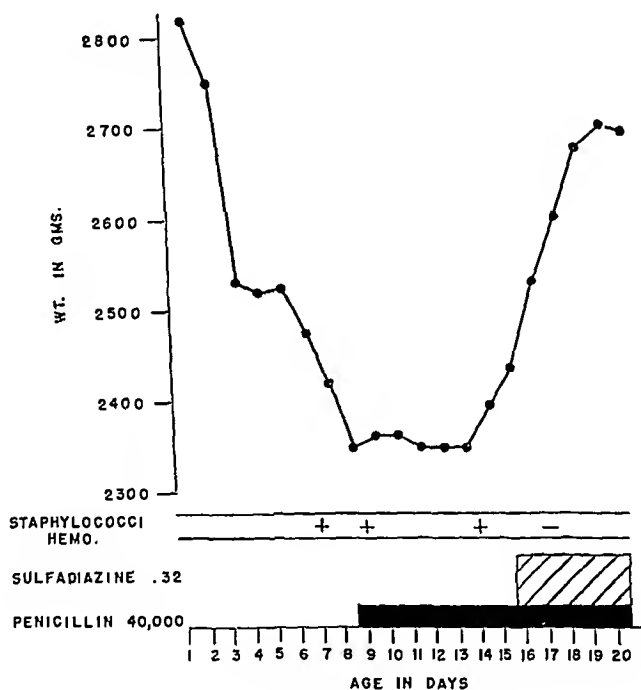


Fig. 6.

CASE 233835.—A white female infant was born Dec. 8, 1946, weighing 3,180 Gm. Delivery followed a normal pregnancy and labor. There were no weight gains for the first seven days. Penicillin 10,000 units q3h was started. A blood culture was not taken until the following day. However, it was positive for hemolytic staphylococci. The weight gains were satisfactory following instigation of penicillin. This therapy was discontinued on the fourteenth day. The infant was discharged on the fifteenth day following a negative blood culture. Follow-up revealed a well baby.

CASE 227302.—A white male infant was born June 19, 1946, weighing 3,490 Gm. Delivery followed a normal pregnancy and labor. Weight gains were unsatisfactory the first eleven days. A blood culture drawn on the eleventh day was reported as positive for hemolytic staphylococci. Penicillin 5,000 units q3h was started. Following this therapy weight gains were satisfactory. A blood culture drawn on the thirteenth hospital day was reported as negative. The infant was discharged on the eighteenth hospital day.

CASE NO. 245947 OCT. 1947

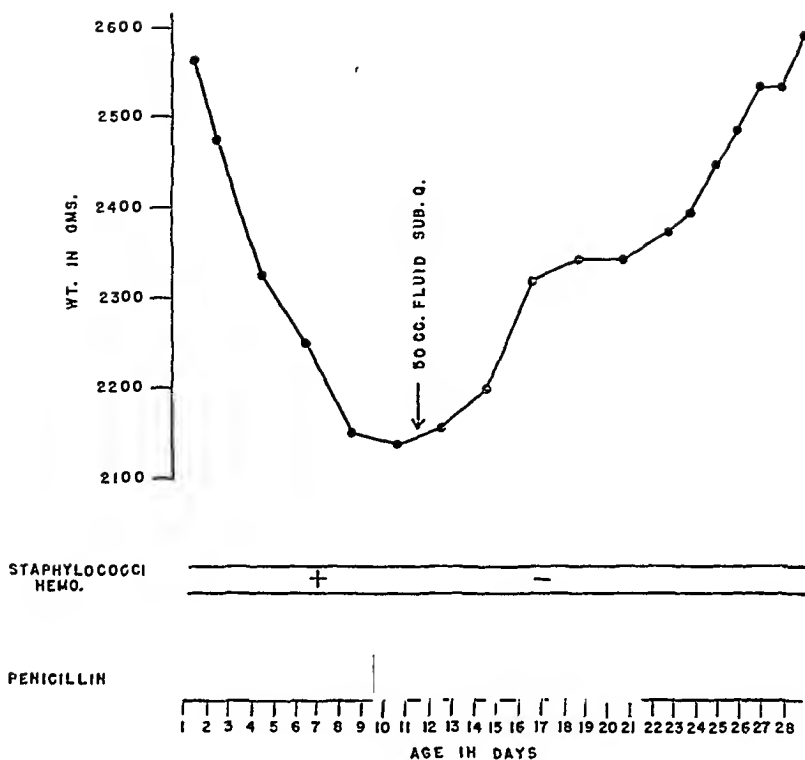


FIG 7.

CASE 232178.—A female Negro infant was born Oct. 27, 1946, weighing 2,310 Gm. Delivery followed a normal pregnancy and labor. Weight loss was progressive for the first twelve days. A blood culture drawn on the tenth day was positive for hemolytic staphylococci. Penicillin 10,000 units intramuscularly q3h was started on the twelfth day. Weight gains were progressive following instigation of this therapy. She was discharged on the thirtieth day following a negative blood culture. Follow up revealed a well baby.

CASE 232076.—A white male infant was born Oct. 24, 1946, weighing 1,956 Gm. Pregnancy was complicated by a premature onset of labor. Nursery course was complicated by anorexia and failure to gain weight. A blood culture drawn on the nineteenth day was positive for hemolytic staphylococci. Penicillin 10,000 units intramuscularly q3h was started on the twenty-second day and continued for seven days. Weight gains were progressive following instigation of this therapy. He was discharged on the fortieth day following a negative blood culture.

CASE 232230.—A white female infant was born Oct. 28, 1946, weighing 2,820 Gm. Pregnancy was complicated by pre-eclampsia and questionable active tuberculosis. Weight gains were unsatisfactory in spite of good appetite. A blood culture drawn on the ninth day was positive for micrococci. A second culture was drawn on the thirteenth day and penicillin 10,000 units q3h intramuscularly was started. The infant's gains improved and penicillin was discontinued on the nineteenth day. The second blood culture was lost. A

CASE NO. 245813 OCT. 1947

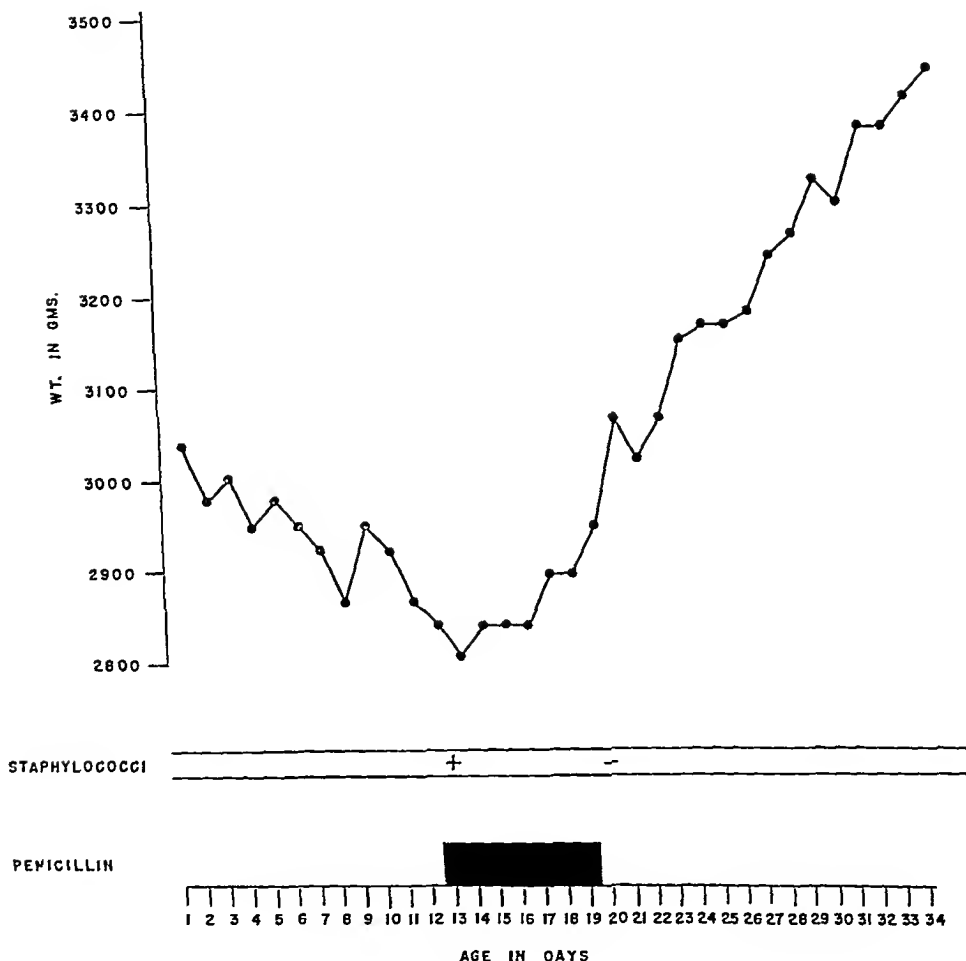


Fig. 8.

third culture drawn on the twentieth day was reported as positive for hemolytic staphylococci. Penicillin 10,000 units q3h was again started. The infant was discharged on the twenty-ninth day following a negative blood culture.

CASE 232293.—A white female infant was born Oct. 30, 1946, weighing 3,650 Gm. Delivery followed a normal pregnancy and labor. On the fifth day she began regurgitating several feedings daily. On the eighth day she began losing weight daily. A blood culture was drawn on the eighth day and reported as positive for hemolytic staphylococci. Penicillin 10,000 units intramuscularly q3h was started on the twelfth day. A second blood culture was drawn on the twelfth day and was again positive for hemolytic staphylococci. Penicillin was discontinued on the seventeenth day, at which time another blood culture was obtained. The infant was discharged on the eighteenth day after five days of progressive weight gains. The third culture was reported as positive for hemolytic staphylo-

cocci. The infant returned to the clinic in two weeks having gained fourteen ounces. A blood culture taken at that time was negative.

CASE 229562.—A white female infant was born Aug. 19, 1946, weighing 2,815 Gm. Delivery followed a normal pregnancy and labor. The infant made only two small weight gains in the first thirteen days. Blood culture drawn on the seventh day was positive for hemolytic staphylococci. Penicillin 5,000 units intramuscularly q3h was started on the ninth day. Blood cultures drawn on the eleventh and fourteenth days were positive for hemolytic staphylococci. Sulfadiazine .065 Gm. q4h was started on the sixteenth day. Penicillin and sulfadiazine were discontinued on the twentieth day, at which time the infant was discharged. Discharge followed six days of progressive weight gains and a negative blood culture. Follow-ups have revealed a healthy child. (See Fig. 6.)

One death occurred in this study. Blood culture was positive for hemolytic staphylococci and peritonitis was thought to be present. At operation eighteen inches of bowel was found to be gangrenous with numerous perforations. In certain other infants signs of illness were of sufficient severity as to cause real concern.

COMMENT

It would seem to be clearly established that the bacterial flora of the skin of newborn infants is unusually rich with members of the staphylococcus group of bacteria as compared to the skin in other age groups. The interpretation of the data described in this report must of necessity be tempered by this fact. It is difficult to believe that the high incidence of positive blood cultures taken for cause and the frequency of positive repeat cultures can be explained solely by contamination from the skin.

Despite the fact that contamination of blood cultures with *Staph. albus* is a very common occurrence, the data recorded here suggest that these same organisms may at times invade the blood stream of certain newborn infants. Contamination from the skin would seem to be an inadequate explanation of the high incidence of positive cultures taken for cause, the regularity with which repeat positive cultures were obtained, the apparent disparity in positive cultures for the various age periods, and the response to therapy.

In suggesting pathogenic and invasive properties to *Staph. albus* we are not unmindful of the fact that this concept is not supported by prevailing opinion. When one considers the scarcity and inconclusive nature of the data pertaining to bacteremia of the newborn infant, prevailing opinion would not appear to be too well supported by fact. The ubiquitous nature of white staphylococci may well account for the unusual frequency with which these organisms are recovered in blood cultures during the neonatal period. The informative study of Torrey and Reese² concerning the aerobic flora present in the upper respiratory passages of newborn infants suggests a possible point of entrance. These investigators found that nonhemolytic *Staph. albus* are generally the first organisms to appear in the throat and nasopharynx of newborn infants. In this area they multiply and grow in abundance. It is not unreasonable to hypothesize that when organisms of low pathogenicity are present in abundance they may well overcome the inadequate defenses available to newborn infants and invade the

blood stream in sufficient numbers to result in the syndrome described in this report. The data recorded here would seem to give support to this conception.

The frequent presence of staphylococci in blood samples of healthy infants seems ample proof of the low pathogenicity of the organisms regularly recovered in blood cultures. It is our present practice to test all staphylococci recovered in blood cultures for their ability to produce coagulase. To date all recovered organisms have failed to produce coagulase with one exception. In this instance the organism was identified as hemolytic *Staph. aureus*.

Regardless of what may be a proper interpretation of the significance of the positive cultures described in this study, response to therapy has been too regular to be considered as apparent rather than real. The administration of penicillin and sulfadiazine in the clinical syndrome described has regularly been followed by clinical improvement. In our nurseries the necessity for infusions and blood transfusions has been greatly curtailed.

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2. Torrey, J. C., and Reese, Martha K.: Am. J. Dis. Child. 69: 208, 1945.

SOCIO-EMOTIONAL FACTORS ACCOUNTING FOR GROWTH FAILURE IN CHILDREN LIVING IN AN INSTITUTION

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SOME twenty-five years ago, Holt and Fales,¹ in a classical paper, remarked "that strikingly good health and excellent nutrition can be maintained" in children obliged to live in an institution. These authors were originally stimulated to study the question because of an impression, then prevalent, that "children living in institutions decline in general health and vitality, and that their growth and physical development are inhibited." Holt and Fales, however, then showed that "this is not a necessary result, and that the contrary may be true."

The factors which those authors stressed as contributing to their good results were: (1) regularity in habits of eating, sleep, rest, and exercise; (2) a simple but liberal diet, and (3) freedom from contact infections. The only reference to possible socio-emotional effects is contained in the statement that the children "were happy and gay, not suffering in the least from institutional repression, although they were living under strict regulations."

Such observations have often been confirmed during ensuing years, for it is generally acknowledged that good health and excellent nutrition can be achieved wherever sound institutional management is exercised.

Important as the elements of physical hygiene, medical supervision, and general management obviously are, they are not of themselves sufficient to assure that children in an institution, or for that matter, anywhere, will grow and develop satisfactorily. In fact, in our experience, a crucial role is played by what may be called, for want of a better term "social and emotional adjustment."

SOCIO-EMOTIONAL CONNECTIONS WITH GROWTH AND GROWTH FAILURE: RECIPROCAL RELATIONS

That good socio-emotional adjustment is a necessary condition for good health and good growth now appears to us as undeniable. This conclusion, of course, is not new, but in this paper we shall demonstrate a means of quickly visualizing this interrelationship.

Though professional and administrative officers of institutions have long been familiar with so-called behavior problems, and even though it is routine practice today to be alerted, by way of admission histories, to such possible problems, the connections between physical growth and mental or emotional adjustment are very widely ignored.

To anticipate somewhat the results that are described in the accompanying case histories, it may be said that close, systematic check on physical growth has proved itself to be very helpful in evaluating over-all progress, in indicating

procedure or treatment, and in supplementing clinical impressions of the physician or observations and conclusions by the psychiatrist, case worker, cottage parent, or supervisor. We have learned that evidence of physical growth failure as determined by the Wetzel Grid² is an indication of the need for further inquiry concerning emotional disturbances, whereas knowledge of emotional or social tensions as revealed by case records or other sources often leads to further investigation of physical progress and development.

Continued growth failure intensifies the search for physical as well as for psychological causes, and, ultimately, for remedial measures that may even call for temporary change of environment, as described in Cases 3 and 4. On the other hand, reports of improved behavior are checked by observations to determine whether improvement in physical growth has likewise taken place, and if not, to ascertain how that, too, may be accomplished.

In general, attention is paid to physical growth and to socio-emotional behavior for the reciprocal benefit that is to be derived from such coordinated observations. As a result, decisions on program can be formulated with much more than usual confidence. If, for instance, emotional unrest is suspected, a monthly check of the child's Grid record is practically certain to disclose whether the suspected condition is sufficient to affect the child's growth. We are quite confident that a serious emotional disturbance in any child would be manifest on the Grid record of growth when pains are taken to keep that record up-to-date by means of quarterly measurements of weight and height. More attention can therefore be concentrated on those children who fail to maintain the Grid standards of acceptable growth (that is, on those who deviate from an established channel by more than one-half channel for each ten levels of forward advance, and/or who fail to progress at the rate of one level line per month).

A given developmental and/or behavior problem is certain to be more distinctly understood and comprehended by all concerned when that problem situation is judged in terms of the concrete effects which a child's Grid displays concerning his physical growth. This is a result that has been noted not merely by the professional staff, physicians, nurses, psychologists, or psychiatrists and social workers, but also by administrative, supervisory, and other staff members.

In brief, to attempt to deal with a socio-emotional problem in this institution, without benefit of Grid control, is to be working too much in the dark. Similarly, those of the staff primarily concerned with physical growth and with the requirements imposed by growth failure are spared the ignoble error of concluding that, "More calories, more vitamins, etc., might be needed," because they are kept informed of what is going on in the socio-emotional realm of such a child.

It is interesting to note that socio-emotional disturbance can at times exert a sufficiently powerful brake on the natural processes of growth and development to offset every other favorable influence that would normally act to promote and to achieve good growth.²³ That is a result which becomes especially plain under the conditions of institutional child care, because it is precisely

²³The use of the Wetzel Grid in pointing out the connection between social and emotional disturbances and growth failure has been discussed in *Health*, Canada's national health magazine of March, 1948, in an article by Dr. Griffith Binning, entitled, "Peace Be On Thy House."

under those conditions that one has a direct, if not an unique, opportunity to witness good growth existing side-by-side with growth failure, some of which may be unbelievably obstinate. What such experience teaches, above all, is that physical growth progress simply cannot be taken for granted in any child; it must be individually checked upon and controlled, no matter how well a given child may ostensibly appear to be or how perfectly living conditions meet every reasonable standard of shelter, comfort, hygiene, food supply, and other needs of child welfare.

Our studies have been made at Bellefaire, The Jewish Children's Home of Cleveland, Ohio, which is an institution for dependent and neglected children, built on a cottage plan, on a 32-acre parcel in the outskirts of the city. The children come from twenty-seven states, and are in need of group living and psychiatric and case-work treatment. Usually they stay for a period not longer than two years. Many of the children have been placed because of divorce, parental rejection, broken homes, and emotional upheavals in their own homes that created disturbances in their personality. Psychiatric service, case work services, recreational facilities, and living in small cottage groups are geared to provide a therapeutic environment.

An attending psychiatrist, pediatrician, dentist, six case workers, eight cottage parent couples, group workers, psychologist, librarian, and about twelve part-time recreational workers, together with an office and maintenance staff, carry out the work of the institution. The professional program is under the supervision of the head resident.* The agency is merged with the Jewish Children's Bureau of Cleveland, a foster home agency, and the executive director of the Jewish Children's Bureau is also the executive director of Bellefaire.

All children come through social agencies who have made a thorough investigation as to whether the child needs this type of care or other social services.

GENERAL RESULTS

Types of Growth Failure.—Ever since the introduction of the Grid into Bellefaire as a "control chart" on growth some six to seven years ago, and more especially during the past three to four years during which the staff has learned to become more "Grid-conscious" we have had the opportunity of observing practically every type and subtype of growth failure which Wetzel has described in earlier publications. For practical purposes, however, the two most commonly observed types are those associated with (A) simple malnutrition, and (B) obesity. Non-nutritional problems arising from infectious disease, endocrine disturbances, allergy, and as a result of hereditary influences, are occasionally encountered.

As regards origin and treatment, it is a mistake to consider any form of growth failure as due solely to physical causes. This warning we have been abundantly able to confirm. In fact, in dealing with the particular population that resides at Bellefaire, one that has suffered known emotional stress, impact, or strain, we find almost no example without some trace of socio-emotional disturbance, even if it is temporary. Consequently, when growth failure

*Dr. Ralph Fried is the attending pediatrician, and Morris F. Mayer the Head Resident of Bellefaire.

of any kind becomes manifest in a child's Grid, we assume, on the basis of experience, that emotional effects exist, and that these among other things must forthwith be completely investigated and treated.

Obviously, in some instances, the socio-emotional element, though existing, might be of minor importance. In others it may prove to be a formidable barrier to physical recovery which will not be completely achieved until satisfactory emotional balance has been established. In a few instances we have found it impossible to effect recovery from physical growth failure, but it is also in those instances that we have not been able to overcome emotional upset. (Cases 2 and 3).

Incidence.—Physical growth varies with population origin, condition on admission, and adjustment to living at the institution. There have been times when, through adverse coincidence of unfavorable circumstances, demonstrable failure has been identified in 70 per cent of the resident population. As a rule, the fraction of children showing significant Grid deviations that are classified as failure of types A and B is about 40 per cent, that is, just slightly more than the one in three that is known to occur among the general population. This is accounted for by the following facts: (1) lag of even two levels behind expected Grid position is counted; that is, the most rigorous Grid standards are used in order that control may thereby be maximized; (2) failure is deliberately looked for and checked upon by quarterly or even by more frequent re-examination, measurement, and Grid plottings; (3) all children are included, that is, recent as well as longer term residents.

For reasons already explained, 75 to 90 per cent of the children when newly admitted show measurable growth failure, usually of type A. Among those who have had six months or more in residence, some evidence of growth failure will be seen in about 15 to 22 per cent. At the present time more than one-half of the total incidence is thus attributable to recent admission. This, however, has not always been the case, because in earlier years, before the advantages of systematic follow-up by the Grid technique had been learned and applied, and during the era in which the tendency to "let nature take her course" held sway, growth failure was about twice to three times as prevalent as now. While it is true that war conditions, notably, constraints imposed by rationing, family separation, casualties, etc., could easily explain 50 per cent or higher incidence, it should be pointed out that "taking growth for granted" was by far the deciding element; for reduction in growth failure to about 22 to 27 per cent of all but recent admissions was accomplished during wartime as soon as Grid control was made to function properly.

In this connection, an incidence of about 50 per cent growth failure has been observed in various private schools. As in our own experience, improvement could likewise be obtained when suitable measures were taken to control a situation that had gotten too far out of hand through the simple assumption that all is well.

In a population of children who have been referred because they are dependent on the institution, the reduction of the incidence of growth failure

below 20 to 25 per cent will require still more perfect and vigorous control of the chief factors which ultimately lead to such failure in the first place. The incidence of unacceptable growth in an institution of our kind could probably be brought down as low as 7 to 10 per cent, if social and emotional disturbance could be more effectively dealt with than the present state of psychotherapeutic development permits.

Responses and Initial Adjustment.—At least two-thirds of all our children show a flourishing "recovery effect" at the second examination three to six months following admission. This is explained, of course, by the fact that living conditions are much more favorable than those under which these children have previously been obliged to reside.

About one-sixth show normally expected progress and the remaining one-sixth a definite decline in the form of physique loss and level lag. In its severer forms this may amount to as much as two and one-half to three channels and the accompanying level lag may increase to fifteen or even twenty levels. Usually however, a deviation of only one to one and one-half channels is found in the first three months together with lag of about four to eight levels.

Subsequent Course.—Not all of those who respond well to their new environment will continue to develop normally at expected rates. About 10 per cent of the children who make rapid adjustment will later develop growth failure in mild form at the time when the first effects of physical rehabilitation have begun to wear off. These episodes, on the whole, are susceptible to almost immediate control when all concerned have had their attention called to the problem. A few children may be a little more difficult to deal with, and will require somewhat longer to regain their established channels and schedules of development. The remainder, about 2 to 5 per cent of the entire population, or about 20 per cent of any given original incoming group, become the chronic problems upon whom the greatest attention must be centered, but for whom, in the long run, practically the least benefit is to be expected or obtained. We have observed that this group of "physical incorrigibles" consists largely of those children who were too disturbed to benefit from treatment. Some of them had to be transferred to state hospitals or special institutions for unusual disturbances.

From a practical standpoint, our general results may therefore be summed up as follows:

1. Initially or during later residence there is, in most of our children with growth failure, a very striking and close parallelism between this physical affliction and socio-emotional adjustment. Onset and recovery in the one is accompanied quite simultaneously by corresponding progress in the other. The great majority of children who show either, show both, and the disturbances are roughly equal, that is, milder and severer forms of physical growth failure are associated with corresponding degrees of emotional trouble.

2. Dissociated failure, in which anomalous social behavior may either precede or follow evidence of physical lag or channel loss, though less frequent than the foregoing, is probably on the whole more demanding and more difficult to deal with.

The two varieties may be explicitly sketched out: e.g., in the one, physical growth failure will only at some later time be found to be caused by previously unobserved socio-emotional handicaps; contrariwise, in the other, known behavior difficulty will be such as to lead, after an interval, to physical growth slowdown. Similar dissociation is observed during the recovery phases; the psychologists, psychiatrists, case workers, and others will, in one instance, report unmistakable improvement in behavior before a corresponding physical change can be confirmed, or finally, the physician may find, in another child, little or nothing to be desired beyond what its growth and development already show, even though that child's social behavior is still far from acceptable as regards his own or his group living.

3. As for prognosis and treatment, we have learned that in this institution for dependent and neglected children physical growth failure could not be corrected by relying on physical means alone. Had that been possible, growth failure should not have appeared at all in an environment where efforts to provide shelter, food, and living enabled a good majority of youngsters, similarly experienced, to grow and develop satisfactorily. Additional calories and vitamins with which to pay off "fuel debts" were never of themselves sufficient to induce and to effect recovery until a feeling of security, and simultaneously with that, emotional tranquility, could also be firmly established.

CASE HISTORIES

To provide concrete illustrations of our main findings, four case histories are reviewed briefly. All show the simple nutritional type of growth failure (A) since this, in our experience is much more troublesome to deal with in emotionally disturbed dependent children than the obese form B. Even as few as four such examples are sufficient to demonstrate (a) that emotional adjustment and physical growth are inseparably related; and (b) that Grid control is a simple and remarkably exact means of helping to check on progress and on results.

These examples taken in order show: (1) prolonged initial adjustment; (2) delayed, intractable, and progressively more serious maladjustment; (3) recurrent failure; and (4) interrupted care, with full recovery on a second admission.

CASE 1.—Paula was 8 years, one month old when she entered Bellefaire shortly after she had been deserted by her mother, who had suffered a psychotic breakdown subsequent to the birth of a deformed child. Up until then, Paula had lived in a fairly well-established family for which the father had shown great interest, and among whom only minor friction took place. Though the mother was emotionally unstable, she had taken good care of the girl. The mother's breakdown had been sudden, the family separation equally so, with the result that it took the child almost two years to become oriented and adjusted to realities.

During the three months following admission Paula was in a daze. Coincidentally she dropped from level 77 to level 69, though failure to eat was not responsible. This loss of eight levels of development actually put her eleven to twelve levels in arrears at the end of that period, because she should have reached level 79 or 80 according to normal expectancy.

She gradually made friends, and was gradually accepted among the children. When

her infant brother was placed in the nursery cottage, she took an interest in him and learned to love him in spite of his deformity. Intensive case work was given during that whole period.

During the mother's convalescence, which took about a year, the father maintained a close and uninterrupted interest in the girl. When the mother returned, recovered from her psychotic episode, she accepted her daughter as she had always done, and was helped to take an interest in the baby. This led to a reunion between father and mother, and thereupon to an awareness on the child's part, that she could soon return to her home. The over-all trends in the Grid record (Fig. 1) closely parallel Paula's progressive adjustment to institutional life, which required a year and one-half to become satisfactorily established.

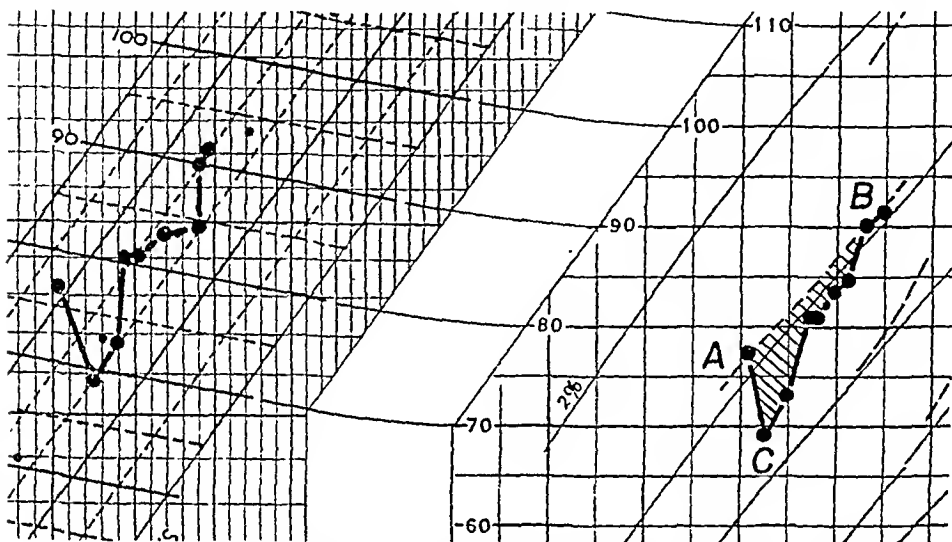


Fig. 1.—Paula. A-C represents the initial growth failure on admission to Bellefnaire. At A Paula was 8 years one month old. At C she was 8 years, 4 months old. C-B represents the recovery period as the child adjusted to Bellefnaire.

It is particularly important to emphasize that the *amount* and *kind* of growth failure which her Grid shows *could not* (and ordinarily would not) be recognized by clinical examination, because she never slipped below channel *M*. Her bodily contours were still such as to inspire the impression of "good nutrition," "good physical condition," etc. In situations such as hers, that conclusion would be erroneous; and it would be so because the comparatively good appearance of children in *M* tends to mask any accompanying failure even when that is as great as Paula's was, and as plainly manifest as it is in her Grid record.

CASE 2.—Sol entered Bellefnaire three days after his seventh birthday, along with his brother who was 11 years old. Both were very bright children; each had an I.Q. of about 140. Their parents had been divorced, an act that confused and disturbed both boys, who were deeply loyal to their father. For the latter reason, the referring agency had recommended institutional rather than foster home placement, but the agency also recommended that institutionalization should be no longer than one and one-half to two years, since it sensed that the boys should not be deprived of the benefit of a private home, this being especially true of the younger.

Sol made a good adjustment during the first year and one-half. Then he had progressively more serious difficulties at Bellefnaire. He started out as, and has continued to be, a leader in his group, whose respect he commanded even though he was one of the smallest boys of the group.

The plan to place him in a foster home after a year and one-half was thwarted by two circumstances: no suitable foster home was then available, and both parents strongly resisted that suggestion. As a result Sol was obliged to remain under institutional care. He showed some behavior disturbances and gradually became involved in various difficulties. He developed a definite negativistic attitude, and for the past two and one-half years has merely been "marking time," in spite of an outward appearance of making a good adjustment to institutional life. All attempts of the social workers and psychiatrists to get close to him, his brother, and his parents, and to arrange foster home placement have thus far been unsuccessful.

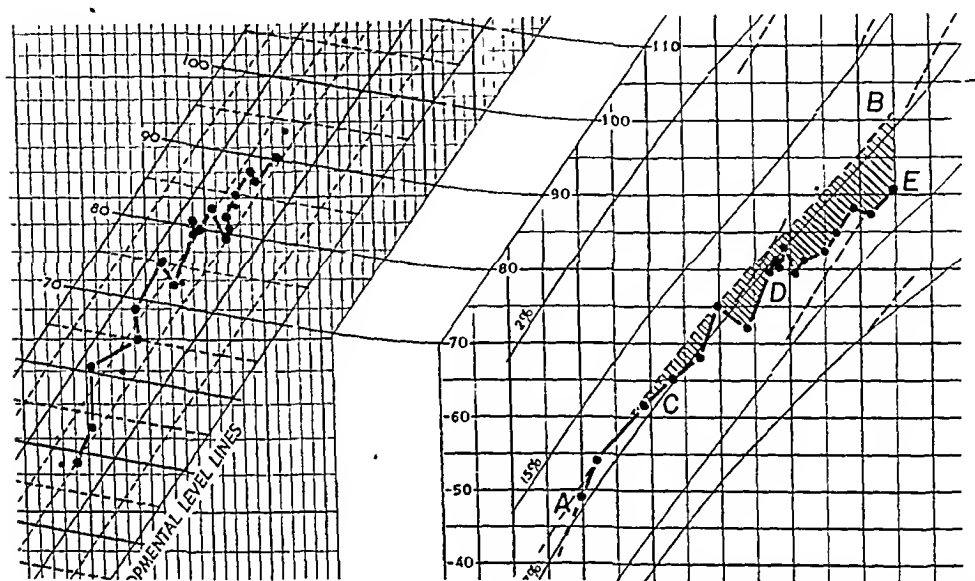


Fig. 2.—Sol. Initial adjustment difficulties at C only institution. D-E represents

eighteen-month period, AC, was good. Minor difficulties when he should definitely have left the institution. AB is the course he should have followed.

Sol's Grid record (Fig. 2) clearly reflects the result of all of the foregoing. From this record it is evident that he should have left the institution at about the age of 9 years, for it is plain that institutional living has not been able to prevent or to overcome what has developed, under the circumstances, into moderate and even moderately severe growth failure. From a practical standpoint, still further trouble is all that can justifiably be expected by continued residence here.

It should be noted that Sol was a boy who progressed along the central *M* channel and that he, accordingly, always gave the impression of being quite sturdy and well built. In fact, when he was examined objectively by several physicians, none suspected that he was actually under par or in a state of growth failure that amounted to six to twelve levels of development.

CASE 3.—Alvin entered Bellefaire when he was 9 years, 11 months old, and shortly after the separation of his parents. The father had been periodically addicted to drink, was a poor provider, and finally deserted the home. The mother was employed in a defense factory, and an older brother was in the service.

During his first six months Alvin seemed to make a good socio-emotional adjustment, and on the physical side, gained thirteen levels in a recovery response that carried him from levels 97 to 110. This clear-cut improvement was apparently due to relief from domination by a particularly strong-willed mother who had "always tried to run his life."

Indeed, his early behavior was characterized by an overly submissive compliance to ordinary rules and regulations. Yet the staff soon suspected that he would prove to be a severe problem because his mother made deliberate efforts to interfere with his institutional adjustment. He became involved in numerous delinquencies and showed no guilt feelings. At the age of 12 years and 3 months he had fallen at least twelve levels (or about a year) behind his own schedule of development. In order to treat this moderate growth failure, which seemed destined to get worse unless things changed radically, he was referred to the Children's Fresh Air Camp of Cleveland, a special institution for children with growth deficiencies.

In spite of only a brief stay there, which had to be terminated in two months because of troublesome behavior, he improved promptly on the physical side, with a gain from level 116 to level 126. (Fig. 3, C-D.)

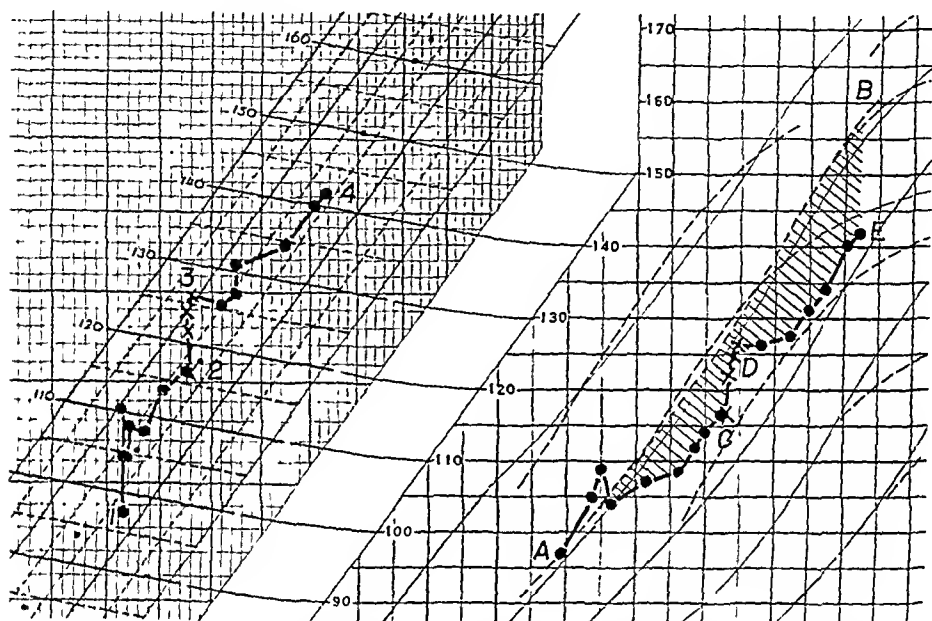


Fig. 3—Alvin. As noted on the chart, the boy's initial response was good. Growth failure starts and continues to point C at which time he was placed on a special health regime in another institution. C-D represents recovery at F.A.C. On return to Bellefaire he continued to fall to point E instead of reaching expected point B.

As definite and as obvious as this response was, it fell about 4 to 6 levels short of complete recovery. His emotional reactions, however, showed no corresponding improvement, with the result that a permanent improvement on the physical side did not occur.

His physical progress halted as promptly as it had previously begun; in the eleven months following readmission he made the "isodevelopmental shift" along levels 126 to 127, gaining, at the most, only one and one-half levels in about a year! He became practically inaccessible to any approach for psychotherapeutics. In this regard, it is noteworthy that he had never been able to form any attachment to an adult during his entire five-year residency here. Lacking such an attachment, he made little more than superficial attempts to improve, and these were, again, overly submissive. Invariably, he fell back into delinquencies and regressive behavior patterns.

In Alvin's case, emotional disturbance and physical growth failure are certainly related as direct cause and effect. It is evident to us that physical means alone cannot succeed in overcoming his growth failure, which becomes ever more serious as he approaches the time of epiphyseal union. In view of the partial recovery he was once enabled to make,

the outlook for full recovery would by no means be unfavorable, but the outcome itself will depend, as much as ever, upon his adjustment in some favorable socio-emotional environment.

Alvin's physical appearance in the examining room belied his true status and progress. He never gave the impression of being actually "under par" though he did look better after his partial recovery to A-126. Without the Grid record he would have been passed repeatedly with negative findings.

CASE 4.—Joseph has been in the institution on two occasions separated by a one and one-half year interval spent in foster homes. His first entry to Bellefaire began when he was 6 years, one month old, and lasted for three years. It was unsuccessful in practically every respect; his second entry, at the age of 10½ years, has now lasted almost two years and it has provided a complete recovery from serious growth failure, as well as an all but complete socio-emotional adjustment to this same environment.

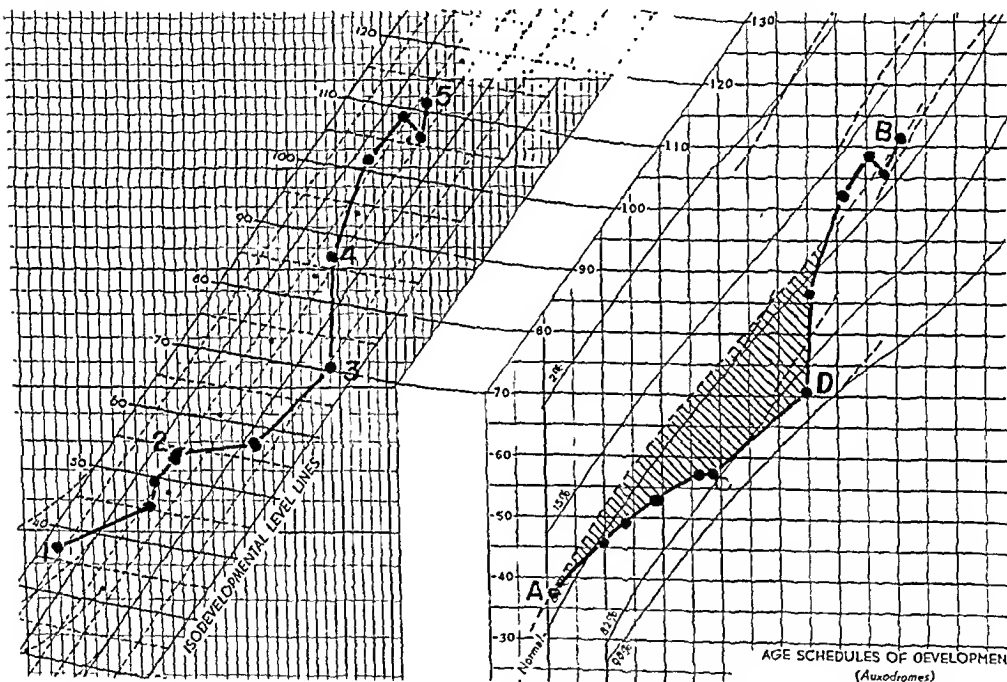


Fig. 4.—Joseph. At A he was 6 years old and his unsuccessful adjustment is shown by growth failure which continued until discharge at C. It continued in his own home and foster homes until D, when he was readmitted to Bellefaire. This time he made a successful adjustment and reached his expected level at B.

Joe, whose father had died when the boy was still an infant, originally entered Bellefaire following a series of failures in foster homes. These were caused primarily by interference of his mother, although she herself had no competence as a homemaker.

Joe was a greatly disturbed and confused boy who could make no really satisfactory adjustment at any time during his first three-year stay. His behavior fluctuated between the extremes of withdrawal on the one hand to hyperactivity and aggression on the other. His life at the institution was repeatedly upset by his mother's interference, which led to many unpleasant experiences. Unhappily, the boy was torn between loyalty to his own and to his cottage mother. The former finally insisted that Joseph and his sister return home, something both children desired to do.

During his first three years at Bellefaire, Joe had progressed from level 36 to 57, that is, only twenty-one levels in thirty-six months, and much farther to the slender side of the

channel system than his earlier course would normally have suggested. He had actually fallen at least twenty levels behind his scheduled development since he should have reached level 77 along his expected autodrome.

His mother's efforts to support and maintain a home for the children lasted only about a year. Joe and his sister were again placed in foster homes, but again without success. Thus, after one and one half years' absence, both returned to Bellefane. Joe was given intensive psychiatric treatment for his known negativism; the case worker took immediate and thorough charge of his social wants, and Joe himself developed a remarkably close attachment to his cottage father. He remained aloof from most people, however, for a long time, but gradually developed a much more acceptable and positive attitude toward others. His delinquencies decreased, his school marks improved, and he obviously became a happier boy. He has actually emerged as one of the leaders of his group, although his adjustment is not yet sufficiently stable to permit him to be a consistent or an always constructive influence among them.

Joseph's physical improvement was even more pronounced than that which he showed on the emotional side. As his Grid shows, his recovery from physical growth failure became complete within eight months of his second admission. It was complete in the sense that he had, even then, returned to par by advancing thirty one levels from 71 to his own channel at level 102.

While psychological and physical changes did take place coincidentally, the former were, on the whole, the more rapid and the more immediately tangible. Once physical repair had set in, moreover, there was every reason to expect all of the psychological improvement he has ultimately shown. Both effects in this instance are, in a sense, the result of a kind of favorable "shakedown" which took place during his temporary absence between admissions. Otherwise, his second entry would more likely have resulted, through memory association, in repetition and furtherance of his original failure. The first admission had not proceeded satisfactorily and Joseph's power to react to efforts that were made to help him had apparently waned, his outside experience with his mother's unsuccessful efforts and with those at foster homes might easily be interpreted as having cleared the air in preparation for renewed life among the institutional group with whom he had been familiar. In any case, socio emotional adjustment, however achieved, was a necessary condition to his recovery from physical growth failure.

DISCUSSION

The foregoing case histories, taken in conjunction with the records of growth progress as revealed by the accompanying Grids, clearly demonstrate the practical value of such direct and objective follow-up. In each example the Grid trends are definite despite the minor fluctuations they contain. There is, accordingly, no difficulty in deciding which deviations are actually significant or which should be considered as accidental.

A single glance, at the time of each successive checkup, reveals the *kind* and the *amount* of progress that has been made, not in the quite meaningless terms of height or weight changes, but rather in concrete effects such as change in physique, level gain, remaining lag, and caloric deficits. The first two of these can be checked by direct examination and inspection of the child, and when so employed, they can help to substantiate clinical impressions. The latter two findings serve as a basis for prognosis and for therapeutic plans. Thus, whether the child's Grid be viewed as a whole, or for separate detail, it registers the net effect not merely of what has been going on or of what has been accomplished, but it indicates to physician, nurse, case worker, and cottage parents alike what still remains to be achieved. Expressed as it is, in

terms of physique and size, direction, and speed of growth, it actually penetrates the external camouflage that is put on by many children at the time of their checkups.

From even the four examples we have described, it is evident that socio-emotional impacts which disturb growth at all are more than ordinarily serious. In the first place, the appearance of growth failure actually demands the solution of two, not simply of one, clinical problem. Second, growth failure, once initiated, always tends to become worse, regardless of cause. From an institutional standpoint, both of these effects imply added responsibility and care, just as they do under normal family circumstances. When, in an institution, some 20 to 30 per cent of the residents are bound to be affected, and it seems unwise to reckon on less than this in a group of dependent children, difficulties of management and control are certain to mount very rapidly, not to mention the extra load imposed on staff time and effort or the inevitable increase in per capita costs.

For these reasons the benefits of early recognition of failure and of continuing evidence on what degree of control is being achieved hardly require further emphasis or explanation. In any case, socio-emotional disturbances are matters of very real concern and they are, for the most part, none too easily dealt with even when they occur or appear to occur alone. When they persist and incite physical growth failure, as they often do, they become matters for still greater concern. In this situation, we have found it advantageous to make use of the reciprocal actions between emotional upset and growth failure for the purposes of achieving what the institution itself had been established to provide. To this end, individual control on growth as exercised through quarterly, or, when necessary, by more frequent Grid follow-up, has been made an essential part of each child's management, supervision, and care.

SUMMARY AND CONCLUSIONS

1. From observations made in an institution that cares for dependent and neglected children, we have been able to demonstrate that socio-emotional adjustment plays not merely an important but actually a crucial role among all the factors that determine individual health and physical well-being.

In the present study (a) anecdotal matter on behavior is supplemented by, and correlated with, (b) medical findings on health, (c) psychiatric evidence, and with (d) quarterly evaluations of physical growth and development, the latter with the aid of the Grid technique described by Wetzel.

2. From combined evidence of this kind, it has become clear that socio-emotional disturbance tends to affect physical growth adversely, and that growth failure so caused is much more frequent and more extensive than is generally recognized.

3. The most favorable conditions of shelter, spacious grounds, food supply, schooling, medical protection, and supervised social life in such an institution are themselves not sufficient to assure good physical growth and development of its children. All these things are as nothing until equable social adjustment

can be established. When, however, that is accomplished, growth and development among institutionalized children proceeds just as satisfactorily as it ever does, and according to the standards of direction and speed indicated by the Grid technique.

4. For obvious reasons, the incidence of simple growth failure is comparatively high among children who are institutionalized owing to dependency or neglect. Among new admissions, it is practically 100 per cent; thereafter, incidence depends (1) on vigilance and proper action, and (2) on the degree to which disturbance can be controlled.

5. Features of initial and delayed adjustments, recurrent failure, and the occasional advantage of change in environment are described in four case histories illustrated with their respective Grid records. The most general result these examples demonstrate is the cause-and-effect reciprocal relation between socio emotional disturbance and physical growth failure.

6. Regarding the Grid technique itself, certain specific advantages have become apparent. Besides serving its original purpose as a "control chart on physical growth" and thereby supplementing clinical estimates of physical condition and progress, the Grid has proved itself valuable as one guide to coordinating the work of the whole institution to the end that the individual's needs may be most effectively met. This means that the Grid helps to confirm the specialized impressions gained by social workers, psychiatrist, pediatrician, nurse, and supervisors, and that it provides these different staff members with a common basis for understanding their common problems. To all of these it has become the simplest and most accurate method of conveying and of making plain what the current end result on growth in any given child should signify. This advantage helps to secure a more intelligent balance between individual and group needs, on the one hand, and institutional program and facilities on the other.

7. Apart from individual consequences, growth failure adds to the burden as well as to the cost of institutional care, and it subtracts from the results which such an institution is intended to achieve. Faced as it is with the difficulties that emotional upsets themselves impose and with the fact that emotional adjustment and physical growth are profoundly related, the need for early recognition of trouble, prompt action, and periodic appraisal is beyond debate. To this end, individual control on growth as exercised through quarterly, or, when necessary, by more frequent Grid follow-up, has been made an essential part of each child's management, supervision, and care.

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FOOD ALLERGY

DEATH IN A SIX-DAY-OLD INFANT

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THE case to be presented in this paper is unique for the following reasons: (1) The child was one of the youngest to die because of food allergy who has ever been reported in the literature. (2) Death was precipitated by allergic shock following the introduction of an amino acid food. (3) Although, since birth the infant had purposely been given such foods as soybean milk and goat's milk (nonallergenic usually), nevertheless he reacted promptly and severely to them. (4) Finally, because of the sibling history, catastrophe was anticipated and, despite forewarning, was apparently unavoidable.

CASE REPORT

J. T., a white male infant, was admitted to the Jewish Hospital on the service of one of us (R. A. S.) Nov. 4, 1946 at 8:30 P.M. The baby was 6 days old and was born at full term. The mother's pregnancy had been uneventful. Delivery was normal. The birth weight was 7 pounds and 2 ounces. The mother had given birth to a baby several years previously—her first—who died twelve days following birth as the result of severe food allergy, manifested by eczema and diarrhea. This first baby had nursed and also had taken evaporated (cow's) milk as complementary feeding. Because of the sibling history, special attention was paid to the management of this newborn baby in an effort to avoid another catastrophe. It was decided to avoid breast and cow's milk feedings altogether, and consequently nonallergenic milk in the form of Mull-Soy (soybean milk) was used. The baby was taken home on the day of birth and placed under the care of a special nurse with the type of milk mentioned. In spite of this planned program, the child immediately began to develop a facial eczema, which became progressively worse. The infant also regurgitated several feedings a day and vomited large quantities of mucus. He started to show some weight loss. Two days later he developed frequent bowel movements, having seven to nine well formed stools in twenty-four hours. The next day the baby began to pass a great deal of mucus by bowel. Weight loss was progressive. The picture looked just as it had with the first baby, in spite of the forewarning. Then goat's milk feedings were tried, but with no improvement. Hospitalization was decided on for the purpose of parenteral feedings.

In the family history, in addition to the death of the sibling, it was significant that the father suffered from asthma and the mother from eczema and neurodermatitis—a strong allergic background from both parents.

Physical examination revealed a very thin, malnourished, white male infant weighing 6 pounds and 8 ounces (loss of 10 ounces in the six days following birth). The rectal temperature was 99° F. The baby was lying rather quietly and in no acute distress. The face, scalp, forehead, and groin were covered with sealy, eczematous patches. A purulent exudate was present in both eyes. The pupils were normal. The auditory canals were filled with scales on the walls and external openings. The posterior wall of the oropharynx was moderately erythematous and showed a purulent exudate. The chest revealed some coarse râles throughout the lung fields. The heart was normal. The abdomen revealed no tenderness. Peristalsis was normal. The liver, spleen, and kidneys were not palpable. The extremities were normal and showed no pathologic reflexes.

The urine was yellow and cloudy with a pH of 7.0. It contained plus two albumin, a faint trace of sugar, and an occasional white blood cell per high power field. The blood contained 18 Gm. of hemoglobin, 5.44 million red blood cells, and 31,200 white blood cells with 68 per cent polymorphonuclear cells and 32 per cent lymphocytes. Of the white cells, 41 per cent were filamentous neutrophils and 59 per cent nonfilamentous.

The baby was immediately given a continuous intramedullary infusion (tibia) of 5 per cent amino acids with 5 per cent dextrose (Amigen)—a total of 500 c.c. slowly at the rate of 10 drops a minute to avoid speed shock. In addition, 2 ounces of 5 per cent glucose in half-strength normal saline were given orally. Oxygen was administered, and ascorbic acid, 25 mg., was given twice daily.

The baby received all the Amigen and two hours later was being prepared for a transfusion, when at 2:15 P.M. (the day following admission) he suddenly expelled frothy, yellowish mucus from the nose and throat. He appeared cyanotic, became stuporous, dyspneic, and in extremis. Aspiration was immediately performed, oxygen was given by mask, and 3 minims of epinephrine (1:1,000) and 2 gr. of caffeine sodium benzoate were injected subcutaneously. There were many bubbling râles audible throughout the chest, and the heart sounds were not audible at this time. After receiving the epinephrine the respirations became deeper, the cyanosis diminished, and fifteen minutes later, when the chest was again examined, the respiratory sounds were quite clear. The heart rate was 66 per minute and the respirations 40 per minute.

At 4:30 P.M., the infant was deeply stuporous and slate-gray in appearance. The eye movements were jerky with several myoclonic contractions of both upper extremities. The respirations were again moist. The heart rate was irregular and 112 per minute. The epinephrine was repeated and heat applied to the extremities. The transfusion of blood had been canceled meanwhile, the baby not having received any at all.

At 5:15 P.M.—less than twenty-four hours after admission—the baby expired.

The clinical impression obtained was that the baby had died from anaphylactic shock precipitated by the Amigen. This was based on the history of the strong allergic background of the parents, plus the sibling death, plus the eczema and diarrhea (allergic reactions to the usually nonallergenic milks), plus the exciting factor (Amigen) which undoubtedly caused the secretion of mucus from the nose, throat, and bowel, and the edema of the lungs, plus the favorable response to the epinephrine, which unfortunately was only temporary and insufficient to avert death.

Autopsy Findings.—At necropsy, a moderately emaciated infant, weighing 2,700 Gm. and 18¾ inches long, showed erythematous, eczematoid, crusted lesions on the face and forehead down to the neck. The nail beds showed marked cyanosis. The lungs revealed emphysematous areas and purplish mottling. On section, there was evidence of much congestion and edema. The gastrointestinal tract showed submucous hemorrhages in the esophagus and congestion of the entire mucosa of the stomach and small and large intestines. There was a great deal of congestion in the liver, spleen, kidneys, adrenals, pancreas, bone marrow, and brain, visible grossly as well as microscopically.

The cause of death was severe allergy. The shock organs were the skin, gastrointestinal tract, lungs, liver, and brain. The immediate cause of death was pulmonary. The lungs showed hemorrhage and edema due to anaphylactic shock.

DISCUSSION

That allergy is common in the newborn infant is not a new concept. Campbell,¹ in reporting 200 cases of allergic children, revealed that 25 per cent had symptoms during the newborn period. Glaser² further noted that the following signs and symptoms were present at birth or shortly afterward in allergic infants: anaphylactic shock from human milk, infantile eczema, cough, colic, vomiting, wheeze, postauricular intertrigo, dry and ichthyotic skin, edema of hands and feet, seborrhea, excessive sneezing, rhinitis, and excessive hunger.

Clein³ reported that the first allergic symptoms appeared in 39 per cent of 100 allergic children in the first month of life, and in 24 per cent, 13 per cent, and 6 per cent respectively in the following three months. The possibility of anaphylaxis caused by human milk is illustrated by two of his cases:

"A newborn infant whose older brother had died of anaphylactic shock after his first breast feeding presented similar symptoms when one drop of his mother's milk was placed on his tongue. He was promptly weaned. One month later, he reacted strongly positive to human breast milk.

"Another infant, on being placed to the breast on the second day of life, went into a state of anaphylactic shock so severe that the head nurse baptized him during the episode. He was resuscitated by epinephrine and artificial respiration. The same thing occurred on the following day when he was given one drop of his mother's milk. He was proved allergic to human milk by skin testing."

McLendon and Jaeger⁴ listed the symptoms in the syndrome of milk intolerance as follows in the order of frequency with which they occur: constipation, anorexia, abdominal discomfort, pallor, fatigue complex with lassitude, disturbed sleep, recurrent diarrhea, respiratory and urinary disturbances. The characteristic features of the history obtained in these cases are: family history of allergy, excessive milk ingestion during the later months of pregnancy, early ingestion of cow's milk by infant, colic syndrome, and frequent formula changes with only transient relief following such changes.

Most allergists and pediatricians feel as Glaser⁵ does, that the best substitute for these allergic infants, whether the offender is human or cow's milk, is soybean milk. He has shown dramatic improvement in his patients where the cow's milk has been eliminated and the substitute given. It did not work in our case, however.

Many investigators in seeking an explanation for sudden death in allergic infants have advanced different concepts. At one time, the cause for sudden, unexplainable death in an infant, whether of an allergic background or not, was attributed to an enlarged thymus. This has of recent years been disproved. Fear⁶ described this so-called concept of status thymolymphaticus or suffocation by a suddenly enlarged thymus gland. The English Status Lymphaticus Investigation Committee, after performing autopsies on 600 newborn infants who had died suddenly, questions the existence of a thymic diathesis and considers these deaths the result of anaphylactic shock.

Davies⁷ in 1940 reported the fatal outcome in three cases of infantile eczema, the children aged 4, 6, and 8 months, respectively. In his cases the following picture was presented: The first definite change noted was restlessness, then dyspnea, and then in some cases Cheyne-Stokes respirations. Vomiting was frequent and convulsions occurred. The temperature became elevated (103° F. or higher rectally). The infants became unconscious, the lips blue, the skin livid, and the extremities cold—all evidence of shock. He attributed

the deaths in large measure to the psychologic trauma of separating the infants from their mothers.

It is interesting to note that some observers like Epstein^{8, 9} believe in the theory of Sulzberger—namely, that where local medication is used extensively for the eczematous lesions, phenol poisoning from coal tar in combination with an interference with cutaneous respiration and the instability of the autonomic nervous system would explain the symptoms as well as the other circumstances of acute death from allergy. (In passing, we wish to state that no tar or any local medicine was used, because we felt that the condition was too widespread and systemic in origin to yield to local therapy.)

Huttinel and Rever¹⁰ compare the clinical picture in fatalities from allergy to the experimental condition in animals and believe that anaphylactic shock would explain the pallor, syncope, dyspnea, and convulsions.

Waldbott¹¹ also confirms this opinion and points out that in all autopsies on patients who have died from allergy the lungs present, uniformly, congestion, extravasation of blood, and edematous fluid. Death is caused by the edema of the lungs and the ensuing asphyxiation, and it is well known that edema is a definite characteristic of allergy and anaphylaxis.

Leopold,¹² pediatric allergist at our hospital, states that soybean sensitivity, although uncommon, does occur. It may well be that there was some hypersensitivity transmitted to the baby via the placental circulation as the result of the mother's diet during her pregnancy. Soybean is found in many items such as bakery goods (bread, cakes, rolls, and crisp crackers), sauces (Heinz and Lea and Perrin's Worcestershire sauce), salad dressings and mayonnaise, pork sausage and lunch meats, candies, Crisco, Spry, and other shortenings, and oleomargarine and other butter substitutes. In addition, Leopold indicates that Amigen, itself, may be a protein offender. Harris and his associates¹³ have reported a case of sensitivity to Amigen (nonfatal) with anaphylactic manifestations in an adult to whom it was given intravenously, following barbiturate poisoning. Leopold points out that Amigen is the product of pancreatic hydrolysis of casein. Although it is theoretically composed of amino acids and polypeptides, only 65 per cent of the nitrogen in Amigen is amino acid nitrogen, the rest being nitrogen of higher amino acid groupings. It is possible that Amigen may contain higher groupings such as proteoses of casein, which may have caused the anaphylaxis in this case. Dr. Robert Cooke, the eminent allergist, has reported allergic reactions to proteoses of milk.

SUMMARY

1. A fatal case of food allergy in an infant 6 days old is presented.
2. Because of the death of a sibling due to similar allergy, trouble was expected. To prevent another death, the infant from the beginning was placed on nonallergenic milk only. In spite of this precaution, he reacted severely.
3. As a last resort, amino acid food was given. This, however, only served to hasten his death by causing further severe protein shock.

CONCLUSION

The most likely inference is that this infant was sensitized to all forms of protein during its fetal life. We took no chances with protein foods which are possible offenders—namely, human and cow's milk—but instead used hypoallergenic milk such as goat's milk and the soya bean variety, assuming that they would be safe. When these failed, simpler proteins such as those found in Amigen were tried, but to no avail. It is axiomatic that protein is essential to life. Since it was impossible to supply it in this case, even in the simplest forms available, without dire results, it is difficult to see what nourishment would have kept alive such an extremely allergic infant.

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ERYTHROCYTE SEDIMENTATION RATE DETERMINATIONS IN POLIOMYELITIS AND OTHER INFECTIONS OF THE CENTRAL NERVOUS SYSTEM AND MENINGES

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INTRODUCTION

THE variability and nonspecificity of the erythrocyte sedimentation rate* are well known.^{1,2} Previous reports^{3,4} have pointed out the variations in the erythrocyte sedimentation rate in acute poliomyelitis but have, at the same time, emphasized the value of this determination as an aid in the diagnosis of the disease. Because of the problems in differential diagnosis which are frequently presented by abnormal findings in the spinal fluid, it was decided to evaluate the sedimentation rate as a diagnostic procedure on all patients who presented clinical evidence of meningeal irritation or who had abnormal spinal fluid findings. The present report is concerned with erythrocyte sedimentation rate determinations on sixty-five poliomyelitis patients during the acute and convalescent phase of their disease and also acute phase sedimentation rate determinations on forty-six patients who had abnormal spinal fluids, some of which presented a problem in diagnosis. Twenty-six patients who had questionable clinical evidence of meningeal irritation or who were thought to have central nervous system disease disproved by lumbar puncture and clinical course were used as controls.

TABLE I. POLIOMYELITIS ERYTHROCYTE SEDIMENTATION RATES*

TYPE POLIOMYE- LITIS	NO. CASES	ESR ELEVATED ON ADMISSION	ESR ELEVATED 1 WEEK AFTER ADMISSION	ESR ELEVATED 2 WEEKS AFTER ADMISSION	ESR NORMAL ON ADMIS- SION, THEN ROSE
Bulbar	11	3	5	2	3 of 8
Paralytic	28	17	7	5	0 of 11
Nonparalytic	26	13	3	1	0 of 13
Total	65	33	15	8	3 of 32

*Because practically all the erythrocyte sedimentation rates had returned to normal by the third determination, only three determinations have been listed in this table.

MATERIALS AND METHODS

Erythrocyte sedimentation rates were performed on all individuals found to have abnormal spinal fluid who entered the Haynes Memorial Hospital during the period from July 1, 1947, to April 30, 1948. Of these, sixty-five (twenty-one adults and forty-four children) had conditions diagnosed as poliomyelitis and forty-six (eighteen adults and twenty-eight children) had abnormal spinal fluid findings due to other causes (See Table II).

From the Evans Memorial and Haynes Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine.

*The terms erythrocyte sedimentation rate, ESR, sedimentation rate, and fall in red blood cells are used synonymously in this report.

TABLE II. ERYTHROCYTE SEDIMENTATION RATE DETERMINATIONS IN INFECTIONS OTHER THAN POLIOMYELITIS

GENERAL TYPE	SPECIFIC TYPE	NO. CASES	ADMISSION ESR'S	
			NO. NORMAL	NO. ELEVATED
Suppurative meningitides	Meningococcus	7	0	7
	M. tuberculosis	3	1	2
	Hemophilus influenzae	7	3	4
	Staphylococcus	2	1	1
	Pneumococcus	1	1	0
	Streptococcus viridans	1	0	1
	Torula	1	1	0
Viral and post-infectious encephalitides	Mumps meningocephalitis	11	8	3
	Post-measles encephalomyelitis	6	2	4
	Post-varicella encephalomyelitis	1	0	1
	Post-rabies vaccine encephalomyelitis	1	1	0
Meningitis due to other causes	"Serous meningitis"	2	0	2
	Lead encephalitis	2	2	0
	Cerebellar hemorrhage	1	1	0
Total		46	21	25

Twenty-six patients (seven adults and nineteen children) who were thought to have clinical evidence of meningeal irritation or central nervous system disease but who were found to have normal spinal fluid were used as controls. The final diagnosis and number of normal and abnormal sedimentation rates at the time of admission to the hospital are listed in Table III. Some of these patients may have had abortive poliomyelitis, but this diagnosis could not be established definitely.

TABLE III. UNCONFIRMED CENTRAL NERVOUS SYSTEM DISEASE SUSPECTS WITH MENINGEAL SYMPTOMS

FINAL DIAGNOSIS	NO. PATIENTS	ADMISSION ERYTHROCYTE SEDIMENTATION RATE	
		NO. NORMAL	NO. ELEVATED
Upper respiratory infection	4	2	1
Hysteria	4	4	0
Myalgia	4	2	2
"La grippe" syndrome	4	1	3
Pneumonia	3	0	3
Bacteremia	1	0	1
Trichinosis	1	0	1
Rheumatic fever	2	1	1
No disease	3	3	0
Total	26	14	12

A modification of the original Westergren⁵ technique was used for the determination of the erythrocyte sedimentation rate; 3.0 ml. of freshly drawn blood were mixed with 0.75 ml. of 3.8 per cent sodium citrate solution and the mixture drawn up in a Westergren tube to a height of 200 mm. and placed upright in a leveled stand. The fall in red blood cells was measured one hour after the test was set up. The normal range of red blood cell sedimentation with this method is 0 to 15 mm. for male subjects and 0 to 20 mm. for female subjects in one hour.

Weekly erythrocyte sedimentation rates were performed on all patients with poliomyelitis. The determinations on patients with other types of central nervous system infections and on those patients suspected of having neurologic disease were performed usually only on admission since the purpose of the determination was to evaluate its early diagnostic significance.

RESULTS

Of sixty-five patients who had a clinical course and spinal fluid changes consistent with the diagnosis of poliomyelitis, thirty-three had elevated sedimentation rates at the time of admission to the hospital. Of these the elevations in three were accounted for by pregnancy, in one by diabetes and in another by pansinusitis. Although many had only slight elevations in their erythrocyte sedimentation rate (1 to 10 mm. above normal), others showed increases as high as 25, 28, and 55 mm. in uncomplicated cases. At the end of the first or second week most of the sedimentation rates had returned to normal levels (See Table I). There was no correlation between the type of poliomyelitis, severity of the disease, or degree of abnormality of the spinal fluid and the sedimentation rate. Only three patients had an elevated rate following a normal admission rate. These findings are in essential agreement with those previously reported for poliomyelitis,³ but are not in agreement with the small number of elevated sedimentation rates in the acute phase of poliomyelitis as reported by Fox and Evrard.⁴

Forty-six patients who had abnormalities of the spinal fluid due to diseases other than poliomyelitis are listed in Table II. Of twenty-two who had bacterial infections involving the meninges, the admission sedimentation rate was elevated in fifteen and normal in seven. Eleven of nineteen postinfectious or viral encephalitides had normal rates while eight were elevated on entry to the hospital. Two of five patients with an abnormal number of cells in the cerebrospinal fluid due to miscellaneous causes had elevated sedimentation rates.

In twenty-six patients who were referred to the hospital with equivocal findings of meningeal irritation but who had no laboratory or clinical evidence of disease of the central nervous system, the ESR was normal in fourteen and elevated in twelve.

DISCUSSION

The variations and nonspecificity of the erythrocyte sedimentation rate are well known. Although it is generally accepted that the erythrocyte sedimentation rate may be either elevated or within normal limits in the early stages of many of the infectious diseases, the value of this determination in early poliomyelitis has been stressed.^{3, 4} Because of the problems of diagnosis which abnormalities of the cerebrospinal fluid may present and also because of the frequent urgency of making a prompt decision as to whether an instance of neurologic disease is viral or bacterial in origin, an attempt has been made to evaluate the erythrocyte sedimentation rate as a diagnostic aid in making such a differentiation. The results of the present study would seem to indicate that in acute poliomyelitis the erythrocyte sedimentation rate initially may be

elevated, but that in general, the uncomplicated course of the disease is usually marked by a normal rate. This is in general agreement with previous reports.^{3, 4} Frequently, however, a case of nonparalytic poliomyelitis with a large number of cells in the spinal fluid early in the disease may raise the possibility of an early bacterial meningitis. It was hoped, early in this study, that the erythrocyte sedimentation rate might help in differentiating viral and bacterial infections: the results obtained indicate, however, that the ESR is an unreliable diagnostic criterion and that the final decision depends on other factors such as the clinical history, physical examination, the character of the spinal fluid, bacteriological findings, and course of the disease. One report⁴ emphasizes the value of the sedimentation rate as a substitute for a lumbar puncture in "polio suspects." Of twenty-six suspected cases of poliomyelitis, fifty-seven per cent showed a normal ESR with normal cerebrospinal fluid; the possibility that some of these cases were abortive poliomyelitis could not be ruled out.

Frequently the problem arises of differentiating between poliomyelitis and other central nervous system infections in which the spinal fluid pleocytosis is mainly mononuclear. We have recently seen two patients who presented this very problem and in whom the final diagnosis was lead encephalitis and mumps meningoencephalitis respectively, in both the erythrocyte sedimentation rate was normal. Similarly, in one of two cases of proved tuberculous meningitis the ESR was within normal limits on admission to the hospital.

Bacterial meningitis usually produces an elevation of the erythrocyte sedimentation rate, but the rate may be normal in the acute phase in some cases, increasing only later in the disease. Usually the differential diagnosis between bacterial and viral infection of the nervous system is not too difficult, since the sugar determination and demonstration of bacteria in the spinal fluid substantiate the diagnosis. Of the twenty-two patients with bacterial meningitis observed in this report, fifteen had elevated erythrocyte sedimentation rates on admission to the hospital.

The ESR determinations in viral and postinfectious encephalitides observed during this study did not follow any predictable pattern and seemed to be somewhat similar to those observed in patients with poliomyelitis (See Table II). Epidemic parotitis is usually accompanied by a normal erythrocyte sedimentation rate and in those cases in which meningoencephalitis developed, no abnormality in the rate of fall of the erythrocytes was noted. The ESR in the encephalitides and meningitides due to other causes showed variable results (Table II).

It has been stressed^{3, 4} that the sedimentation rate is of value in differentiating between rheumatic fever and poliomyelitis. Since the cerebrospinal fluid examination and sedimentation rate may be within normal limits in certain cases of rheumatic fever and poliomyelitis, it can easily be seen that one cannot rely on either of these determinations to make a diagnosis. Probably the most reliable method of making a diagnosis of either of these diseases, when in doubt, is to follow the course of the disease and rely on the clinical manifestations such as joint pains, heart findings, choreiform movements, paralyses, etc. It can easily

be seen that reliance on the sedimentation rate can be misleading in the differentiation of some cases of rheumatic fever and poliomyelitis.

The value of the erythrocyte sedimentation rate as a diagnostic tool in disease of the nervous system is limited. The results of this study indicate that this determination is of no value in determining the viral or bacterial etiology of neurologic infections in which there is spinal fluid pleocytosis. A thorough cytologic, chemical, and bacteriologic examination of the cerebrospinal fluid is indicated in all cases of suspected infection of the nervous system.

SUMMARY AND CONCLUSIONS

1. In uncomplicated poliomyelitis and other viral infections of the central nervous system the erythrocyte sedimentation rate is elevated in about 50 per cent of the cases at the beginning of the disease.

2. The erythrocyte sedimentation rate is unreliable in differentiating poliomyelitis from other infections of the central nervous system which simulate it.

3. No correlation could be established between the clinical type of poliomyelitis, the severity of the disease or the degree of abnormality of the spinal fluid, and the elevation of the sedimentation rate.

4. The differentiation of viral and bacterial neurologic infections cannot be made on the basis of the sedimentation rate value.

5. The erythrocyte sedimentation rate should never be used as a substitute for a diagnostic lumbar puncture.

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A PRELIMINARY REPORT ON RHEUMATIC FEVER IN VIRGINIA

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IT IS the purpose of this study to investigate the detailed circumstances of 225 cases of rheumatic fever seen in Virginia. Each of the patients has been followed at least three years or until death. We felt that the study of the race, sex, family history, preceding illness, season and age at time of onset of each attack, symptoms, physical signs, laboratory studies, and duration of each attack would lead to a clearer picture of the disease in this locality. The residual cardiac status of the patients, relationship of attacks to removal of tonsils and adenoids, average duration of the disease, and deaths have also been tabulated.

INTRODUCTION

The Virginia rheumatic fever program was initiated in May, 1940, administered under the State Crippled Children's Bureau, and operated on Federal funds. It was developed and has been maintained in accordance with the general policies outlined by the Children's Bureau Advisory Committee. This program has now been in operation seven and one-half years. Because relatively little has been known or written about the disease of rheumatic fever as seen in children in this state, we have, from the beginning, placed emphasis on careful and consistent history-taking and complete and repeated physical examinations. While it is realized that our period of observation is much too brief at this stage to point up anything in the way of prophylaxis, treatment, or ultimate prognosis, we do believe that a clearer picture of the disease, as it occurs in children in this southern state, is beginning to emerge. We, therefore, present our findings to date in this preliminary report.

As of June 1, 1947, a total of 1,205 patients had been seen in the Richmond clinic. Two hundred and twenty-five of these had been definitely diagnosed as having rheumatic fever and had been followed for at least three years. By a careful study of this latter group we have attempted to determine the similarities and differences between the disease here and in other geographic locations, which have been reported at length previously.¹

It is well recognized that in such a protracted disease no final conclusions can be drawn in this relatively brief period of time. However, while the minimum period of known rheumatic fever duration was six months in two patients who died, only those living who were known to have had the disease for at least three years were included. The maximum duration was nineteen years, and the average, 5.95 years. Most of the patients (87 per cent) were seen here while the disease was active, but 13 per cent were referred for observation while the disease was inactive. All patients were under 21 years of age, as those exceeding this limit were referred elsewhere.

¹From the Pediatric Department, Medical College of Virginia, and the Virginia State Health Department.

Read before the Richmond Academy of Medicine, Jan. 13, 1948.

It was felt that the period studied was adequate to fulfil one of our main purposes. This was, namely, to assist the practitioners in this section of the country in making an earlier diagnosis by a tabulation of the relative frequency of the cardinal early symptoms as seen here. While it will be shown that joint aches and pains in the extremities were among the most frequent early symptoms, many cases would be missed if acutely swollen joints were required for diagnosis. We found this condition in only 43 per cent of our cases. It used to be said that acute rheumatic fever was rare in Virginia, and yet old rheumatic heart disease was commonly recognized.

DIAGNOSIS

What then are the criteria for diagnosis? Leo Taran,² in his extensive studies with rheumatic children in New York, has written at length on the laboratory and clinical criteria of rheumatic carditis in children. We have, since the beginning of this clinic, followed approximately the same method of study in an attempt to arrive at a correct diagnosis and later to evaluate activity. The complete study included a careful history, physical examination with special attention to the heart, complete blood count, sickling preparation, urinalysis, stool examination, sedimentation rate, electrocardiogram, and x-ray or fluoroscopic examination. On the basis of these findings the patient was carefully considered. Only if at least one major manifestation, such as polyarthritis, carditis, chorea, old history of rheumatic fever, or nodules, was present with several of the minor ones, such as fever, rash, leg aches, abdominal pain, epistaxis, leucocytosis, elevated sedimentation rate, and anemia, was the diagnosis made.

In determining the duration of activity, Taran's ten points were emphasized. He weighs leucocytosis, anemia, sedimentation rate, pulse rate, fever, vital capacity, weight gain, A-V conduction, auscultatory evidence, and finally clinical observation as to fatigability and emotional stability. Emotional instability continued in 25 per cent when all other laboratory studies were normal. We are impressed frequently, as he was, that "the so-called quiescent interval might be considered as a form of mild rheumatic activity, presenting none of the classical and accepted criteria for rheumatic activity. . . . The final decision as regards the presence or absence of active rheumatic disease rests upon clinical judgment. This, as in all other medical problems, is a product of continued and careful observation and examination of large numbers of children with rheumatic disease over the entire period of rheumatic activity and for years following the active episode."

DIFFERENTIAL DIAGNOSIS AND SELECTION OF CASES

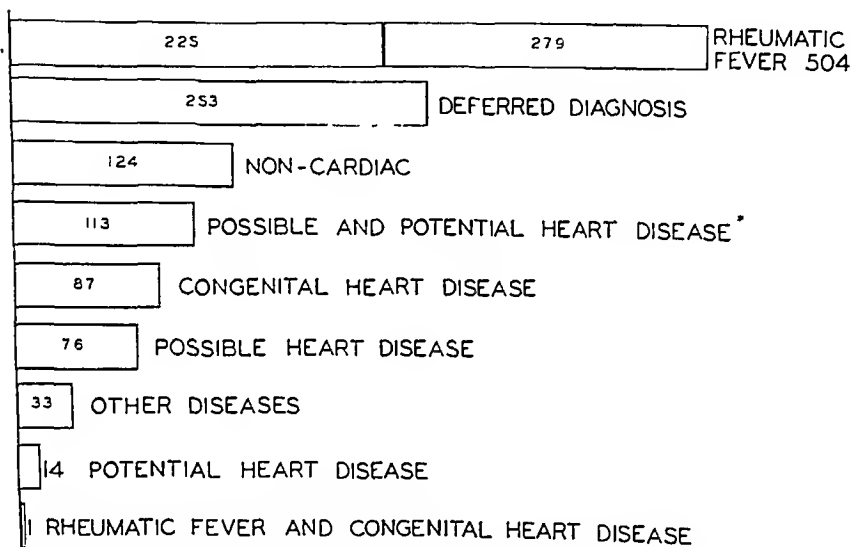
As might be expected in a clinic designed for the diagnosis and treatment of rheumatic fever, in only about 40 per cent of the patients was that diagnosis made. No patients were seen except when referred by a physician as having suspected heart disease or rheumatic fever. Fig 1 illustrates the distribution of cases. Of the 504 patients with rheumatic fever, 225 had had the disease at least three years or had died earlier, and this is the group on which the

detailed study of incidence and manifestations is based. The other 279 developed the disease after January, 1944, and will be studied later after the course of their illness has been followed for a longer period.

In 253, who are listed as being deferred cases, it was the opinion of the examining physicians that sufficient positive criteria for diagnosis had not been obtained for making a final judgment. This group is constantly being changed to one of the other categories. Later work should place most of them in some definite class.

TOTAL CASE LOAD MAY 1940 — JANUARY 1947 = 1205

DIFFERENTIAL DIAGNOSIS



* POSSIBLE HEART DISEASE PATIENTS WITH SYMPTOMS OR SIGNS REFERABLE TO THE HEART, BUT IN WHOM A DIAGNOSIS OF CARDIAC DISEASE IS UNCERTAIN

POTENTIAL HEART DISEASE PATIENTS WITHOUT HEART DISEASE, WHOM IT IS ADVISABLE TO FOLLOW BECAUSE OF THE PRESENCE OR HISTORY OF AN ETIOLOGICAL OR SUSPECTED ETIOLOGICAL FACTOR WHICH MIGHT CAUSE HEART DISEASE

Fig. 1.

The noncardiac patients comprised about 10 per cent of those referred to the clinic. There were 124 of these children in our total of 1,205.

"Possible and potential heart disease" was the diagnosis in about 9 per cent. As the American Heart Association classification indicates,³ "possible heart disease" is the term used for patients who show abnormal signs or symptoms referable to the heart but in whom the diagnosis of heart disease is uncertain. "Potential heart disease" is reserved for patients without circulatory disease whom it is advisable to follow because of the presence or history of an etiological factor which might cause disease. As noted in Fig. 1, those with either possible or potential heart disease alone comprised a smaller group.

The patients with congenital heart disease made up 7.2 per cent of the total. One case was felt to be rheumatic fever superimposed on congenital heart disease.

Among the thirty-three other diagnoses, sickle cell anemia was the most frequent. This disease may so closely simulate rheumatic fever that routine sickle cell preparations are made on every new Negro patient admitted. Nephritis, rheumatoid arthritis, and tuberculosis were each seen in three or four cases. The remaining single cases are listed in Table I.

TABLE I. OTHER DIAGNOSES

DIAGNOSIS	NO. OF CASES
Sickle cell anemia	13
Nephritis	4
Rheumatoid arthritis	3
Tuberculosis	3
Amyelostomiasis	1
Hyperthyroidism	1
Periarthritis nodosa	1
Acquired syphilis	1
Congenital syphilis	1
Lymphoblastoma	1
Hypothyroidism	1
Multiple myeloma	1
Leucemia	1
Infantile kidney	1

INCIDENCE: RACE, SEX, FAMILY HISTORY

In the City of Richmond the 1946 census gives a total population of 222,908, with 70 per cent white and 30 per cent Negro. The 37 per cent Negro patients in our group is, therefore, somewhat higher than the percentage of Negroes in the general population. Paul and others,⁴ in their New Haven study, concluded that rheumatic fever is less common in Negroes but more virulent when it does attack. It is recognized that many more white patients than Negroes are treated by private physicians without referral to the central clinic. Ash,⁵ in Philadelphia, found 83 per cent white and 17 per cent Negro with about equal division of white and Negro admissions.

The sexes were almost evenly divided, with 51.5 per cent females and 48.5 per cent males in our group. Coombs⁶ found in his outpatient work in Bristol that almost two-thirds of his patients were females. Gibson⁷ notes an incidence in girls of almost 2 to 1. Paul⁸ observed that below the age of 13 girls are more often affected, while in adults men are. In over 1,500 patients Cohn and Lingg⁹ found, as we did, that the sexes were affected in almost equal numbers. Fig. 2 illustrates our incidence figures.

In taking the history, an attempt was made to elicit the family history of (1) any heart disease, (2) rheumatic fever, (3) arthritis, or (4) allergy in the siblings, parents, uncles, aunts, or grandparents. Of the 225 in our series, fifty-two were aware of some type of heart disease, the specific type often not known. In thirty-nine cases (17.3 per cent) there was rheumatic fever in the family. Arthritis was reported in nineteen families, and allergy in eight others.

In Gibson's⁷ series of 1,487 cases a rheumatic family history was obtained in 16.3 per cent, which varies only one per cent from our series. Histories are admittedly far from reliable, as parents remember little of their own illnesses and often have no medical attention for them. Other authors have found a much higher incidence, such as Coombs,⁶ who obtained a positive family history in almost half of his cases. Wilson and Schweitzer¹⁰ also found about one-half of their families to have positive histories. In the New Haven study, 21 per cent of Paul's⁸ group of 122 families were rheumatic. They conclude that a rheumatic patient with negative parents has a 10 per cent chance of having rheumatic offspring. If a rheumatic child of a rheumatic parent is chosen, his chances of having rheumatic children are about 25 per cent.⁴

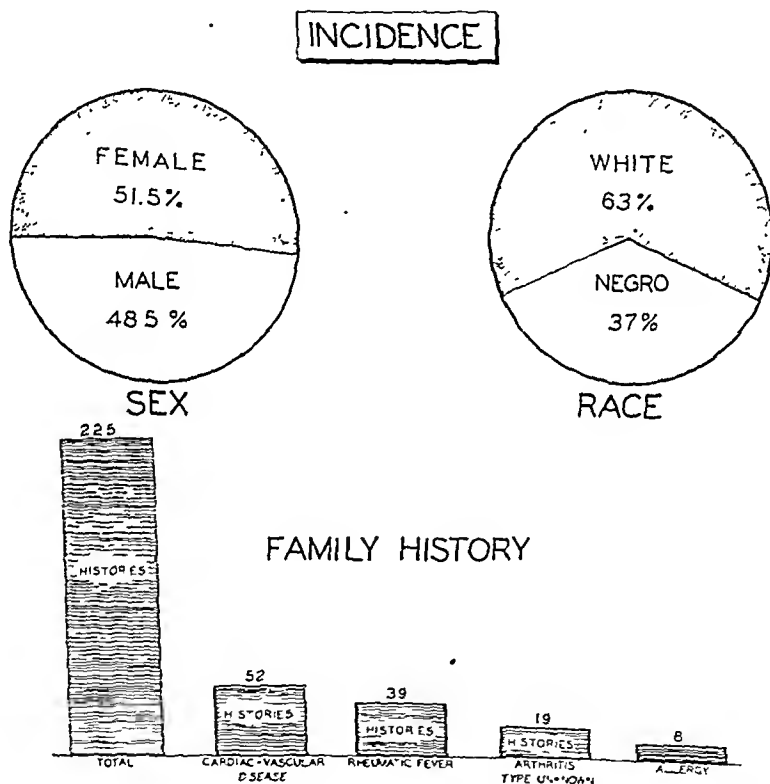


FIG. 2.

AGE

The Metropolitan Life Insurance Company's graph¹¹ based on Hedley's survey demonstrates the striking age susceptibility from 5 to 15 years. As Fig. 3 shows, we had a few patients in whom the onset occurred before 5 years of age. There is a sharp upward turn then, with a peak at 6 years. The significance of a second peak at 15 years is not clear. It is true that we did see a fair number of patients in their teens, but after 15 there is a sharp decline. Our average age

of onset was 7.87 years, which was very close to that found by others. Stroud¹ and Wilson and his associates¹² found it to be 7.3 years, while Paul¹³ finds it to be 7 years. Coombs⁶ gives a higher average age—namely, 10.2 years.

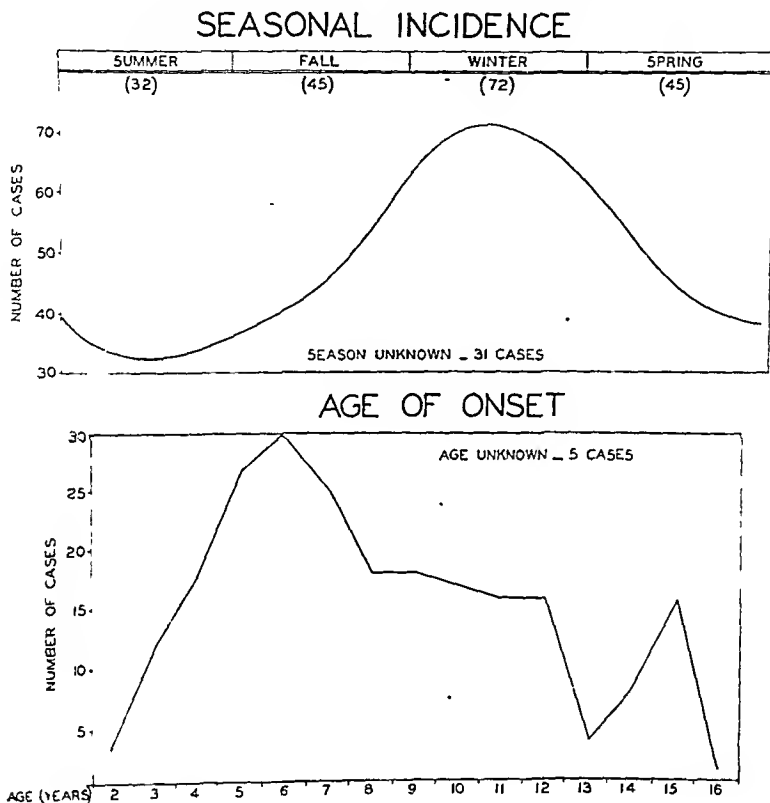


Fig. 3.

SEASON

The seasonal incidence was of special interest. Gibson,⁷ in summarizing 1,135 attacks, both primary and recurrent, found a high point in April. This has been true for the country as a whole. The peak in our 225 cases was in January. The initial attacks occurred in the winter in seventy-three cases. Autumn and spring were about equally divided with forty-six and forty-eight cases respectively, with the lowest point in the summer (thirty-seven cases). Actually, November, December, and January were our months of highest incidence, with April and July being next, as Table II illustrates.

The season for second or later attacks was about the same. There were eighty-five in the winter, fifty-four in the spring, forty-two in the fall, and thirty-five in the summer. Again January was by far the most prominent single month.

All this is in keeping with the observation of Stroud and his associates¹ that the farther north you go, the later the high point. They say: "Coombs finds

the incidence maximal in England during the months of December and January; Levine finds the maximum in Boston during February; we find it maximal in Philadelphia during March; and the observations of Swift and Wilson suggest it may be maximal in New York later in the spring."

TABLE II. MONTH OF ONSET

MONTH	FIRST ATTACK	LATER ATTACKS
January	35	38
February	17	28
March	11	18
April	18	21
May	9	15
June	10	13
July	18	14
August	9	8
September	13	15
October	14	12
November	19	15
December	21	19
Unknown	31	20

ILLNESS PRECEDING INITIAL ATTACK

In looking for a clue as to the true etiology of rheumatic fever, much has been studied about the illness preceding the initial and subsequent episodes. In a few cases the preceding illness of the patients in our series was seen by our hospital staff, but in most instances it was necessary to rely on the history or the notes of the referring physician. That rheumatic fever often follows untreated cases of streptococcic sore throat with high antistreptolysin titers was shown by recent army reports.¹⁴ There are volumes of evidence pointing to the relationship of rheumatic fever to the hemolytic streptococci, but reinfections by streptococci do not always reactivate the disease, even in patients with rheumatic heart disease.⁸ The work summarized by Kuttner¹⁵ on prophylactic sulfonamides in patients with inactive cases gives the striking agreement of seven

TABLE III. ILLNESS PRECEDING INITIAL ATTACK

ILLNESS	NO. CASES
Sore throat	98
Scarlet fever	9
Tonsillectomy	5
Other:	
Pneumonia	6
Influenza	2
Colds	2
Measles	2
G.C. vaginitis	2
Chicken pox	2
Burns	1
Sinus infection	1
Urinary infection	1
Infectious hepatitis	1
Pertussis	1
Impetigo	1
Nephritis	1
Diphtheria	1

clinics as to their value in prophylaxis. She concluded that this proved the importance of Group A beta hemolytic streptococci as a factor in the etiology. Jones and Massell¹⁶ believe it is the volume of the streptococcal infection which is important rather than the particular type, from their studies on immune bodies and other phases of the disease.

Table III shows that in a little less than half of our patients a history was obtained of a sore throat or streptococcal infection preceding the onset of rheumatic fever. Nine cases of rheumatic fever were preceded by scarlet fever, six by pneumonia, and one each by a urinary or skin infection. Five occurred shortly after a tonsillectomy. Most of the other preceding illnesses were probably coincidental, but they are listed in Table III. Jones and Mote¹⁷ found a cold or sore throat preceded the initial attack in 58 per cent of their series of cases, which agrees closely with our findings.

The history of tonsillectomy and adenoidectomy previous to the primary manifestations was found in thirty of 141 of the carefully studied patients of Stroud and his associates,¹ while ninety-two of the 141 developed symptoms before tonsillectomy and adenoidectomy were done.

Only 20 per cent of our patients had a tonsillectomy and adenoidectomy before the onset of the first episode. Thirty-three per cent had the operation after the disease was considered quiescent. In 47 per cent it has not been done.

Kaiser¹⁸ and Mackie¹⁹ show larger groups of cases, all of which suggest that first attacks of rheumatic manifestations occur from 34 to 50 per cent less often in tonsillectomized groups than in nontonsillectomized groups.

SYMPTOMS OF INITIAL ATTACK

Every effort has been made to elicit a true and complete picture of the symptoms of the first and later episodes by detailed history-taking. In the presence of any one of the cardinal manifestations of polyarthrititis, carditis, chorea, or nodules, the diagnosis is clear. But the more elusive symptoms are found frequently to predominate in our series and call attention to an illness in which the carditis appears later. Joint pains head the list, as shown in Fig. 4, 157 of the 225 patients having joint pains in the initial attack. Fifty-nine patients experienced pain only, while 98 were acutely swollen. Sixty-eight showed no joint symptoms. One hundred and seven of our patients suffered aching of the extremities without joint involvement. Colm and Lingg⁹ recognized the problem which faces any clinician who sees suspected rheumatic fever: "As initial phenomenon for dating the onset of rheumatic fever the meaning of muscle and joint pains has often been called in question. How to be certain when they are significant is difficult." They found true polyarthrititis in 40.3 per cent, and muscle and joint pains in 9 per cent of their series. Muscle pains are less impressive than joint aches, and the latter are considered significant only when additional evidence for a diagnosis is given. Wilson²⁰ found growing and joint pain in 26 per cent and polyarthrititis in 22 per cent of her cases.

Fever was a dominant symptom occurring in 146 patients of our series. It is likely that had the patients all been observed more carefully it would have been seen even more frequently than the histories indicate.

The generalized symptoms of illness, such as malaise, fatigue, anorexia, pallor, irritability, and weight loss, were important in the parents' minds, as Fig. 4 indicates. Obviously, these are not diagnostic of rheumatic fever, but frequently were reasons for seeking medical attention in the absence of striking joint symptoms. The diagnosis was definite in sixty-eight of our patients in whom there was no joint involvement, with usually the more vague symptoms leading to the discovery of a carditis. Severe abdominal pains were noted in eighty-eight. Several were sent to the hospital as having suspected appendicitis.

SYMPTOMS — FIRST ATTACK

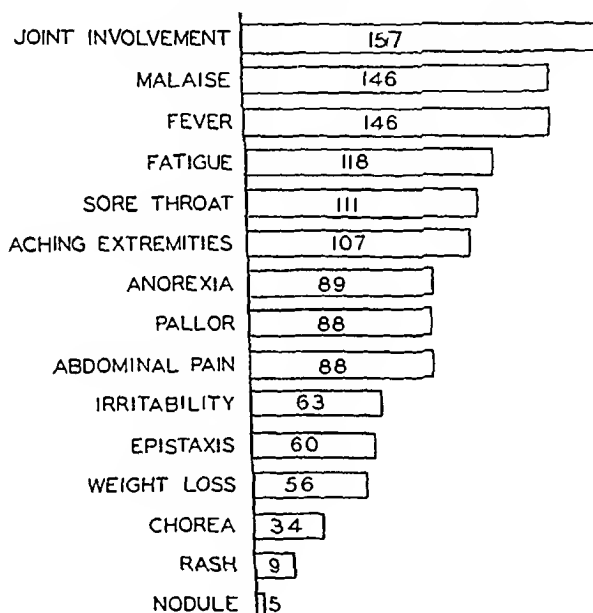


Fig. 4.

TABLE IV. SYMPTOMS DURING INITIAL ATTACK

SYMPTOMS	DURING FIRST MONTH ONLY	LASTING BEYOND FIRST MONTH OR STARTING AFTER FIRST MONTH
Fever	56	105
Malaise	31	103
Pallor	16	77
Anorexia	25	68
Weight loss	19	36
Irritability	7	57
Fatigue	26	102
Abdominal pain	31	66
Aching extremities	27	96
Joint involvement	64	91
Rash	9	10
Epistaxis	24	41
Sore throat	50	67
Chorea	7	29
Nodules	1	4

A sore throat was a definite symptom in 111 patients and was frequently recurrent. Epistaxis was a feature in sixty children. In 15.1 per cent, or 34 cases, chorea was seen as an initial manifestation. Wilson²⁰ found 23 per cent with chorea, and Cohn and Lingg⁹ record only 9.9 per cent.

A history of a rheumatic rash was elicited in nineteen of our patients. Nodules were seen in only five, or 2.2 per cent.

Table IV represents an attempt to note any difference in symptoms between the first and later months of the initial attack. Almost all the symptoms persisted beyond the first month or became more evident in the second or later months. This is as might be expected with a disease of such a chronic nature.

SYMPTOMS—SECOND ATTACK

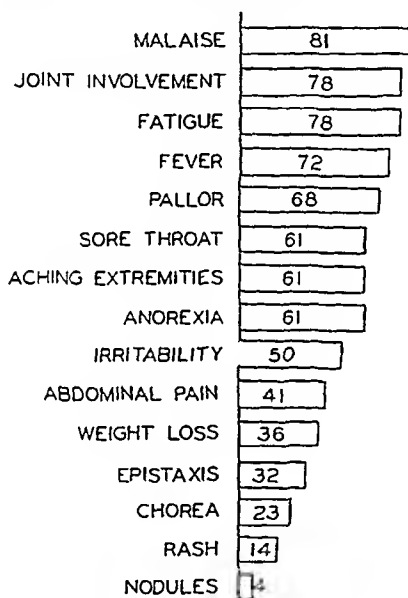


Fig. 5.

SYMPTOMS OF SECOND ATTACK

The symptoms of the second attack did not differ profoundly from those of the first (Fig. 5). Malaise and fatigue feature most prominently, but joint involvement was noted in seventy-eight of the 136 children who had more than one episode. Since eighty-nine of our patients had only a single attack, the total incidence of each symptom in the second attack is decreased proportionately. However, the relative order of frequency of sore throat, aching extremities, anorexia, abdominal pains, pallor, epistaxis, chorea, rash, and nodules is parallel.

In Wilson's²⁰ study of recurrences, which she noted in 85 per cent of 673 patients, growing and joint pains were seen in 26 per cent and true polyarthritis in 15 per cent. We found some joint symptoms in an even higher percentage, namely, 58 per cent. She noted chorea in 21 per cent and we, in 16 per cent.

LABORATORY FINDINGS

The laboratory findings have received varying degrees of emphasis. Ever since Schilling suggested that acute infections or exacerbations are reflected in the hemogram while latent infections are sometimes expressed better with the sedimentation reading, this latter has received special attention with rheumatic fever. Fig. 6 shows the relative incidence of a sedimentation rate over 10 mm. an hour, white blood count over 10,000 and hemoglobin below 70 per cent. The first column shows exactly 100 children in whom the sedimentation rate was over 10 mm. Only eleven patients showed no rise. In 114 children the initial rate was not known. This test was more helpful than the leucocyte count, which was known to be elevated above 10,000 in only forty-one cases or 18 per cent. In 50 per cent it was not known, and in 32 per cent it was under 10,000. Wilson's²⁰ figures suggest that the greatest degree of leucocytosis occurs with the acute carditis, while chorea, joint pains, etc., show a lower range.

LABORATORY TESTS

FIRST ATTACK

SECOND ATTACK

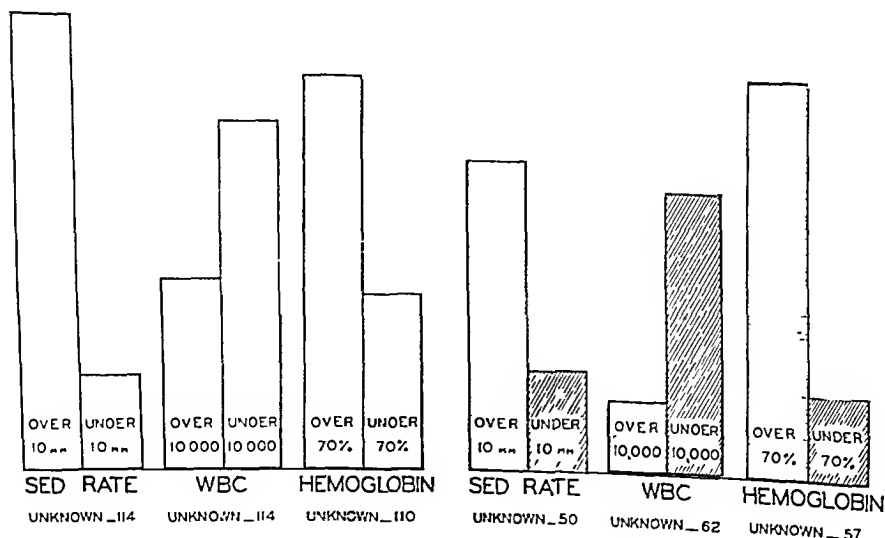


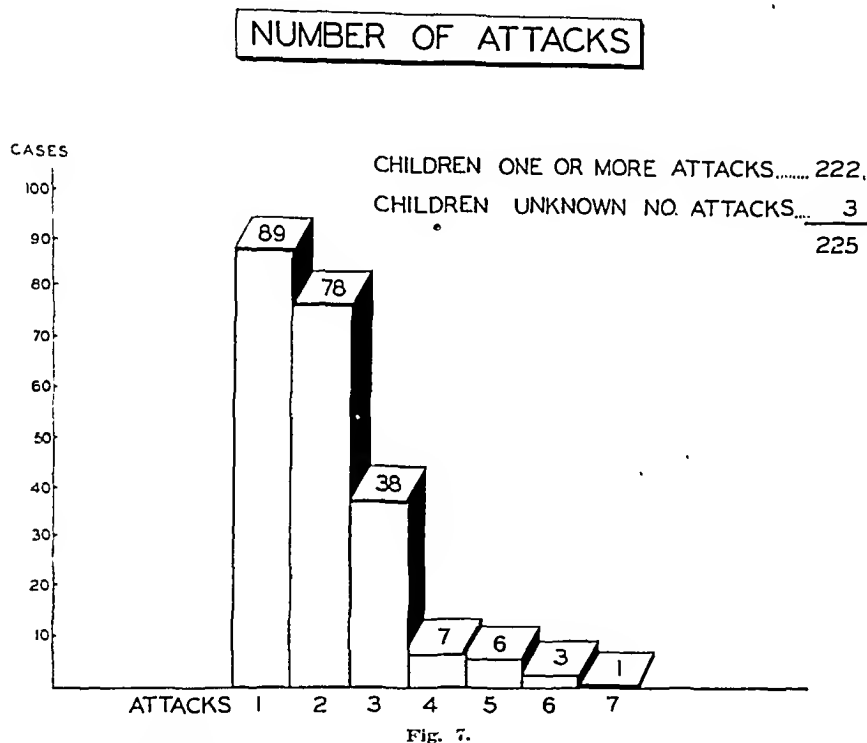
Fig. 6

The secondary anemia which was often present during rheumatic activity is usually related to the severity and duration of the manifestation of the disease. Wilson²⁰ reported an average hemoglobin of 12 Gm. on patients admitted to the New York hospital. When seen by us, 18 per cent showed anemia with hemoglobin less than 70 per cent (15.6 Gm. standard). In about 50 per cent the hemoglobin was not known. Seventy-five children had no marked anemia.

The laboratory tests in second attacks of our series followed practically the same pattern with less striking leucocytosis and anemia.

NUMBER OF ATTACKS

During a period averaging eight years following the onset of the disease, 85 per cent of Wilson's²⁰ patients had one or more recurrences, whereas Cohn and Lingg⁹ noted 75 per cent recurrences in their series of 3,129 cases. In both groups the greatest number of recurrences was between the ages of 5 and 14, and it was felt that puberty was of greatest importance in cessation of exacerbations.



In our period of study, 61 per cent had recurrences. Of the 225 children, 39 per cent (eighty-nine) had one attack. Almost as many (seventy-eight) had two attacks and thirty-eight had three attacks. As shown in Fig. 7, there were seventeen patients who had more than three episodes. The patient who suffered seven attacks was followed in the Medical College of Virginia Hospital during each of these episodes.

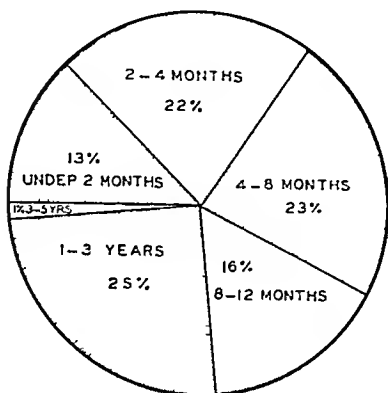
TABLE V. COMPARISON OF RECURRENCES IN TWO SERIES

NO. ATTACKS	OUR SERIES	COHN & LINGG ⁹
	%	%
1	61	75
2	34	51
3	17	32
4	3	20
5 or more	4.4	12

The percentage of recurrences seen thus far in our series as compared with the series of Cohn and Lingg is given in Table V. In our series the recurrences will probably rise as the period of follow-up lengthens. Thus far, the average duration of the disease is 5.95 years.

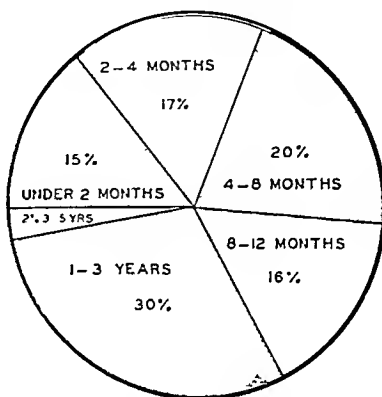
DURATION OF ATTACKS

FIRST ATTACK



MEAN DURATION OF ATTACK
= 6+ MONTHS

SECOND ATTACK



MEAN DURATION OF ATTACK
= 8- MONTHS

Fig. 8.

DURATION OF ATTACK

One of the most difficult quantities to measure in such a study is the duration of each episode of rheumatic fever. At each successive clinic visit, in addition to a history and physical examination, the usual laboratory and other tests suggested by Taran and others were repeated to attempt to gauge objectively the continuation of activity. Taran² estimates 25 per cent of his patients have continued activity which can be detected only by clinical judgment. In the opinion of the clinician in charge, the mean duration of the first attacks in our patients was just over six months. Fig. 8 illustrates the percentage in each group. In about 50 per cent the disease was inactive in six months. In 26 per cent the disease was active for more than one year.

For the second episode, the mean duration of attack was just under eight months. In about 50 per cent it lasted eight months, and in 32 per cent, longer than one year.

CARDIAC INVOLVEMENT

If it were not for the cardiac involvement in rheumatic fever, it would be considered in a class with other acute febrile illnesses and of little serious con-

sequence. But knowing that carditis in some form was found in all but four of Wilson's²⁹ 673 children and that Ash's⁵ tabulation of a group of over 3,500 cases showed it in 60 to 79 per cent, we are forced to pay heed to suspicious preliminary symptoms. Cardiac involvement is used most often to refer to murmurs which were considered significant, abnormal sounds, enlargement or unusual contour of the heart, or electrocardiogram changes (Table VI). One or more of these abnormal factors was found in 188 or 83 per cent of our patients during the first or later attacks (Fig. 9). Of these 188 children, 132 showed changes during the original episode and fifty-six were added during later ones.

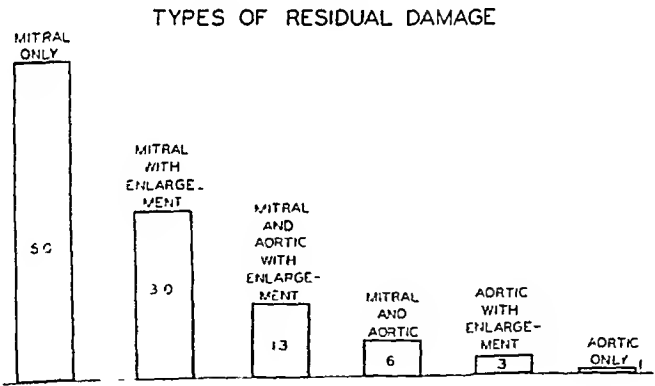
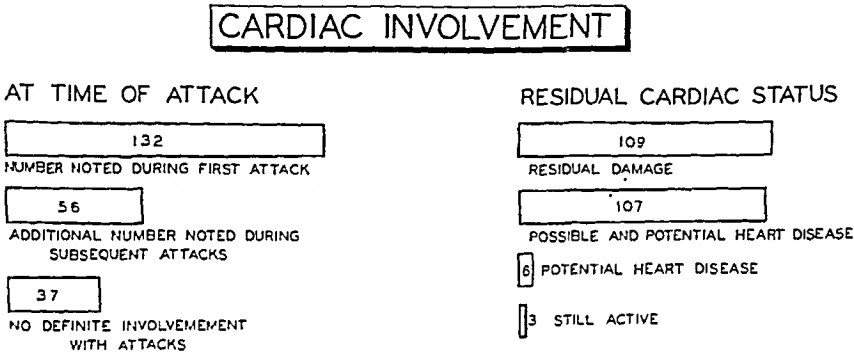


FIG. 9.

TABLE VI. HEART INVOLVEMENT IN INITIAL ATTACK

INVOLVEMENT	NO. OF CASES
Systolic murmur	107
Diastolic murmur	21
Abnormal sounds	14
Thrill	3
Enlargement of heart	40
Abnormal ECG	46
Abnormal cardiac contour	33
Cardiac failure	5
Friction rub	7

In thirty-seven cases, or 17 per cent, there was no definite evidence of carditis. Jones and Bland²¹ found the incidence of heart disease to be 86 per cent in a series of 518 patients followed for eight years.

An evaluation of our 225 patients in repeated examinations revealed that of the 188 who had shown carditis with the exacerbations, 109, or 48 per cent of the total, showed residual cardiac damage. Fifty per cent are listed to date as having possible and/or potential heart disease, based on the American Heart Association's classification previously defined.

The types of residual damage are further elaborated at the bottom of Fig. 9. By far the greatest number are mitral lesions (eighty-five cases) with or without enlargement. Mitral and aortic insufficiency with enlargement comprised thirteen cases. Mitral and aortic insufficiency without enlargement totaled six cases. Single aortic lesions without mitral involvement were found in four cases.

DEATHS — 16 OR 7.1%

NEGRO	8
WHITE	8

RACE

M	9
F	7

SEX

1	LESS THAN 5 YEARS
10	5-10 YEARS
4	OVER 10 YEARS
1	UNKNOWN

AGE OF ONSET

1	UNKNOWN
1	6 ATTACKS
1	4 ATTACKS
2	3 ATTACKS
7	2 ATTACKS
4	1 ATTACK

NUMBER OF ATTACKS

LESIONS

INSUFFICIENCY AND STENOSIS	INSUFFICIENCY	STE NO SIS
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MITRAL DISEASE — 12

AORTIC DISEASE ALONE — 0

4	MITRAL AND AORTIC LESIONS
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CAUSES OF DEATH

RHEUMATIC FEVER	
ACTIVE	INACTIVE
WITH CARDIAC FAILURE — 8	TETANUS — 1
WITHOUT CARDIAC ENLARGEMENT — 4	POST T AND A — 1
AFTER SULFA DRUG — 1	BRONCHOPNEUMONIA — 1

AVERAGE DURATION OF LIFE
AFTER ONSET OF RHEUMATIC
FEVER — 40.8 MONTHS.

FIG. 10.

DEATHS

Our period of observation is admittedly insufficient for comparison with other figures as to death rates. Fig. 10 is presented solely to show the pertinent features of the disease as it occurred in sixteen children (7.1 per cent of our patients) who have died thus far. Similar to the series as a whole, these patients are about equally divided according to race and sex. The age of onset was 5 to 10 years in two-thirds of them. All but four had more than one attack.

Three-fourths of them had mitral disease, and one-fourth had both mitral and aortic involvement.

In three cases death could not be attributed directly to rheumatic fever. Tetanus, bronchopneumonia, and an anesthetic used with tonsillectomy and adenoidectomy were believed to be the responsible factors. In thirteen cases the disease was demonstrably active, and it was complicated by cardiac failure in 50 per cent.

The average duration of life in these sixteen children after the onset of rheumatic fever was just over three years.

It is interesting to note that in all but two cases there was a history of joint involvement. The other symptoms were not unlike those previously listed in order of frequency.

SUMMARY

1. Of a total of 1,205 patients referred by physicians to the Medical College of Virginia Rheumatic Fever Clinic from April, 1940, to June, 1947, as having probable rheumatic fever or heart disease, 504 had the diagnosis of rheumatic fever confirmed, while 203 were being followed as possible and/or potential heart disease, and 253 were still being listed as deferred.

2. Two hundred and twenty-five, or 44 per cent of the 504 patients, were the subjects of special study since they had been followed for at least three years or until death.

3. The study of this group of 225 patients brought out the following facts: The average duration of the disease was 5.95 years as followed thus far. The sexes were about evenly divided.

Race incidence closely paralleled the percentage distribution in population.

A family history of rheumatic fever was obtained in 17.3 per cent.

The average age of onset of initial manifestations was 7.97 years.

January was the peak month for onset in both the initial and recurrent episodes.

A history of preceding streptococcal infection was obtained in about 50 per cent of the children. Only 20 per cent had had tonsillectomies prior to the onset of the disease.

Joint pains led the list in frequency of symptoms occurring with initial and secondary attacks. Fever and malaise ran close seconds.

Laboratory findings as to elevation of sedimentation rate, leucocytosis, and anemia were somewhat helpful but far from conclusive.

Sixty-one per cent had one or more recurrent episodes while under observation.

As nearly as could be estimated, the mean duration of the first attack was 6.4 months, and that of the second was slightly under eight months.

Cardiac involvement was demonstrable in 83 per cent of all patients during the active stages of the disease. Only 49 per cent showed demonstrable residual cardiac damage, but the rest are still under observation as having possible and/or potential heart disease.

Seven and one-tenth per cent (sixteen patients) died during the period of observation. The average duration of life after onset of the disease in these children was 40.8 months.

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Case Reports

POLIOMYELITIS IN A THREE-WEEK-OLD INFANT

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THE rarity of poliomyelitis in infants under 6 months of age prompts the reporting of this case. A review of the English literature reveals the youngest patient with poliomyelitis on record to be in a 2-week-old infant in the 1907 New York epidemic.⁵ More recently Biermann and Piszczek³ reported a case of poliomyelitis contracted on the eleventh day of life with fatal termination on the sixty-seventh day. The infant had been exposed for ten minutes to its mother, who showed clinical signs of poliomyelitis on the first post-partum day and died three days thereafter. Hess and Levinson⁸ report the disease occurring in a 4-month-old infant and diagnosed in the preparalytic stage. A 6-year-old sibling had been stricken with a case of fulminating poliomyelitis eight days prior to the onset in the infant. Recovery in the infant was without sequelae. Lubchenco and associates,⁹ in a statistical study of the 120 cases occurring at the Children's Hospital, Denver, during 1943, found the youngest child attacked to be 4 months of age. Five cases of poliomyelitis in infants are found recorded in foreign literature.^{1, 2, 7, 10, 12}

It is generally accepted that until about the sixth month of age infants possess a passive immunity to poliomyelitis similar to the immunity demonstrated to diphtheria. The foundation for this belief is the work of Aycock and Kramer² who showed that serum from the cord blood of ten out of twelve newborn infants possessed the same neutralization power to poliomyelitis virus as did the blood serum of their mothers.

The following report is of a case of meningopolioencephalitis in a 3-week-old infant.

CASE REPORT

Clinical Findings.—The patient, R. H., was born on Sept. 21, 1947, delivery being uneventful. On October 8 (seventeenth day of life), he began to cry continuously, developed a fever, and appeared to have difficulty in swallowing when fed. He became drowsy and unresponsive to all stimuli and on October 12 was admitted to the hospital where physical examination revealed a very lethargic child who responded only to light stimuli. Respirations were 65 per minute, with a pulse of 120 per minute and a temperature of 100.5° F. The body was completely flaccid; the gag reflex was absent, and an effort was made to suck on the tongue blade. The chest and heart were normal. Petechiae which blanched on pressure were noted over both lower extremities.

Laboratory Data.—The red blood cell count was 4.95 million cells per cubic millimeter of blood, and the white blood cell count was 12,550 cells per cubic millimeter of blood. The differential white blood cell count showed 57 per cent of the cells present to be polymorphonuclear neutrophils with 35 per cent lymphocytes and 8 per cent monocytes. A lumbar puncture was productive of clear spinal fluid under normal pressure. The spinal fluid gave a 3 plus Pandy reaction and was found to contain many red blood cells and 15 white blood cells per cubic millimeter of spinal fluid. The carbon-dioxide combining power of the blood was 57 volumes per cent. The blood sugar was 102 mg. per cent; the non-protein nitrogen was 65 mg. per cent and the creatinine 2.6 mg. per cent.

From the Departments of Laboratories and Pediatrics, Mount Sinai Hospital of Cleveland.

Course in the Hospital.—On admission the child was given penicillin and caffeine sodium benzoate and placed in an oxygen tent. Respirations soon became Cheyne-Stokes in character. The baby went rapidly downhill and died twenty-four hours after admission, four and one-half days after the onset of symptoms.

Postmortem Findings.—An autopsy was performed one and one-half hours after death. Unfortunately, permission was not obtained for removal of the entire spinal cord. The body was that of a well-developed and well-nourished white male infant weighing 3,630 Gm. and measuring 68 cm. crown-heel length. The lips and nail beds were cyanotic, but otherwise there was nothing of note on the external surface.



Fig 1—Section from the cerebral cortex showing infiltration of the meninges by lymphocytes and mononuclear cells.

Examination of the body cavities revealed the mesenteric lymph nodes to be moderately enlarged and the thymus pale and slightly edematous. Examination of the organs was essentially negative except for a partial pulmonary atelectasis.

There was slight prominence of the parietal bosses; the fontanelles were neither tense nor depressed. The brain weighed 560 grams (average normal weight, 380 grams). The meninges were smooth and glistening. There was moderate cerebral edema present with slight flattening of the gyri. The sub-arachnoid vessels were injected to a moderate degree. On sectioning the brain, the tissue appeared paler than usual with little differentiation of grey and white matter. Edema was evidenced by compression of the ventricles. The small amount of cervical spinal cord which was taken with the brain showed nothing of note grossly.

Microscopic sections from the cerebrum showed the leptomeninges edematous and infiltrated by numerous lymphocytes, plasma cells, mononuclear cells, and

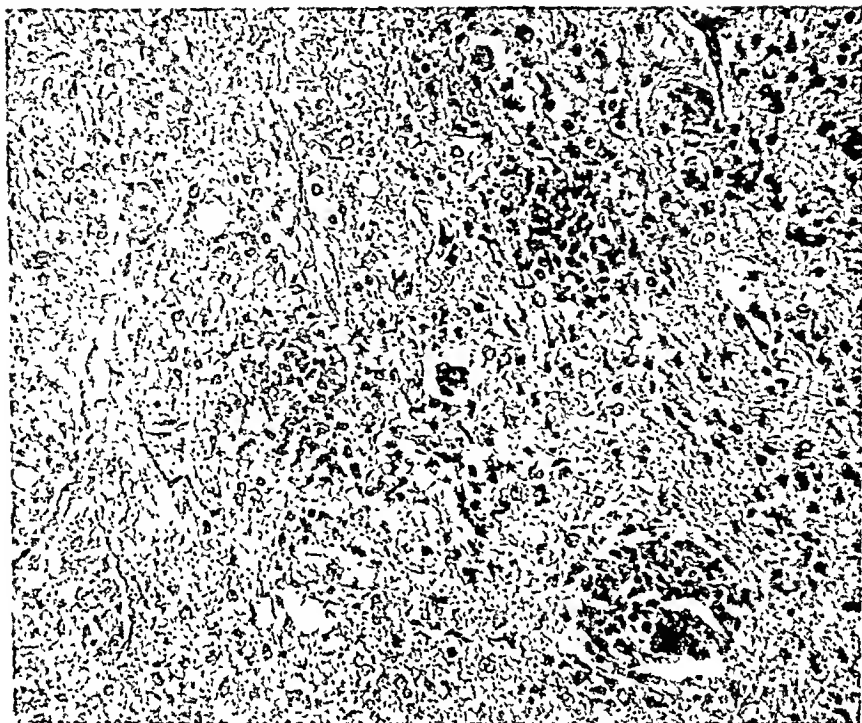


Fig. 2.—Section from the thalamus showing perivascular cuffing by lymphocytes and foci of inflammatory cells throughout the brain tissue.

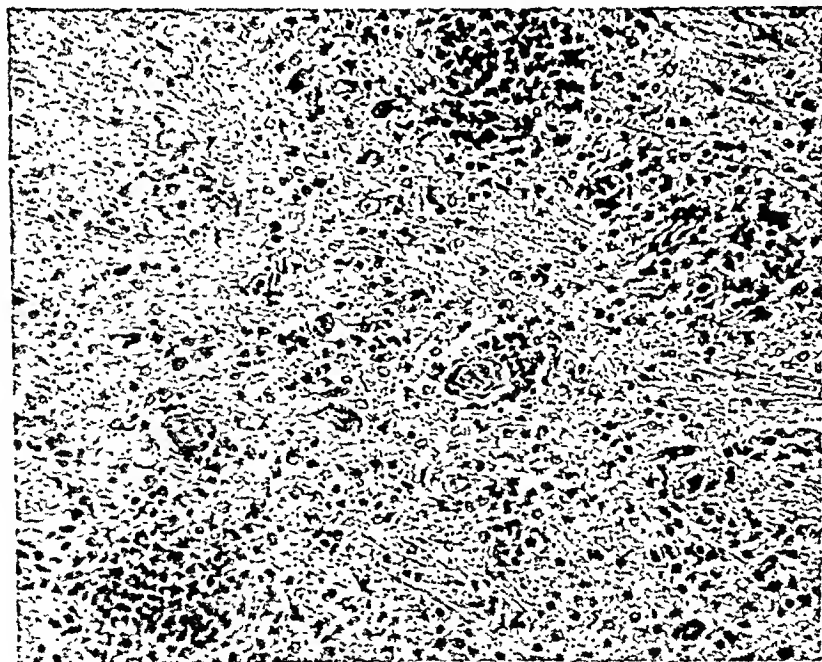


Fig. 3.—Section from the upper cervical spinal cord showing foci of lymphocytes similar to those seen in Fig. 2.

occasional polymorphonuclear neutrophils. The subarachnoid vessels were engorged, as were the cerebral vessels. There was dilatation of the Virchow-Robin spaces with perivascular cuffing by lymphocytes (Fig. 1). Small foci of lymphocytes were scattered throughout the cerebrum, thalamus, and cerebellum (Fig. 2). Similar changes were found in the upper cervical spinal cord. Degeneration of the ganglion cells of the anterior horns was seen but without evident neuronophagia (Fig. 3).

Microscopic examination of lymph nodes removed from the mesentery showed the usual reactive phenomena of edema, vascular engorgement, and dilatation of sinuses with mobilization of mononuclear cells (Fig. 4).

Microscopic examination of all other tissues revealed nothing of significance except for cloudy swelling and fatty change of parenchymatous organs.

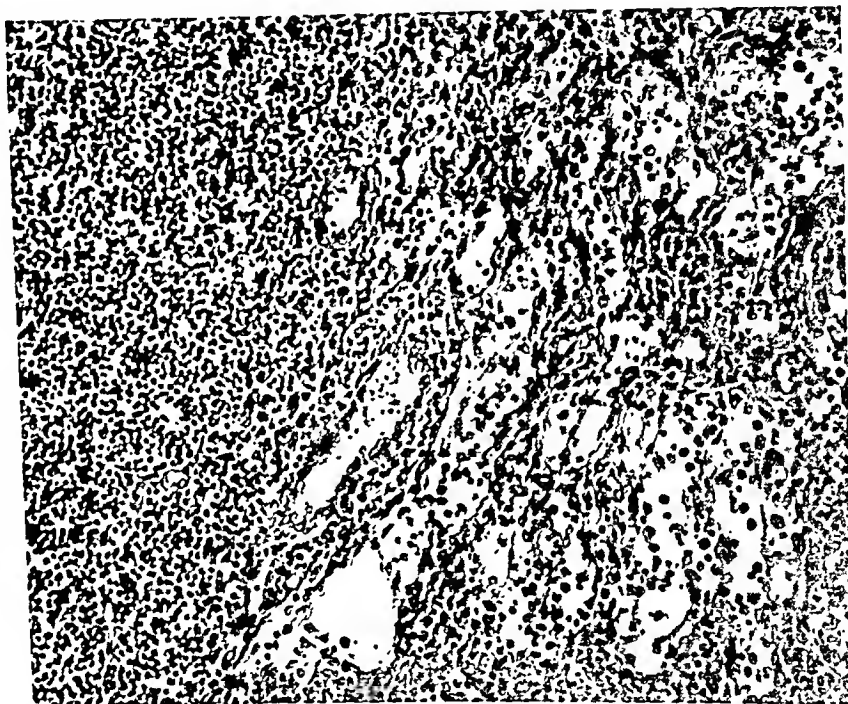


Fig. 4.—Section from a mesenteric lymph node showing marked dilatation of sinuses with moderate numbers of infiltrating monocytes present.

Discussion.—It was interesting to trace the probable source of infection in this case. Both the patient and his 4-year-old brother were exposed to a 13-month-old neighbor on Sept. 26, 1947. The neighbor became ill on September 29 and was hospitalized on October 1 at Lakewood Hospital where a diagnosis of poliomyelitis was made. He was transferred on October 6 to The Cleveland City Hospital where he died on October 14 after having spent the previous twenty-four hours in a respirator. Death was due to meningopolioencephalitis.

The patient's brother became ill on October 3 and on October 5 was diagnosed as having poliomyelitis by his physician who sent him to The Cleveland City Hospital where the diagnosis was confirmed. He suffered permanent residua of the disease with extensive involvement of the muscles of the trunk and lower extremities necessitating the use of braces and crutches for locomotion.

It is impossible to state whether the source of the disease in the patient was his brother or his neighbor, but probably the neighbor served as the common source of infection. A 2-year-old sister exposed to both brothers but not to the neighbor did not develop the disease.

Lubchenco⁹ in the study of poliomyelitis at Children's Hospital, Denver, found multiple infections in nine families, with four cases in one family and three cases in another. It was noted that the first case occurring in each family was the most severe. Gebhardt and McKay⁶ found forty-five cases occurring in twenty families, with thirty-two of the cases having a simultaneous onset or onset within five days after the other sibling developed poliomyelitis. These authors feel that in most instances multiple cases have their origin in a common source of infection.

SUMMARY

A fatal case of meningopolioencephalitis is reported in a 3-week-old infant whose older sibling likewise contracted the disease, both cases possibly having a common source of infection in a fatal case occurring in a neighbor. Four cases of poliomyelitis in infants under 6 months of age reported in the English literature are reviewed.

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HEMORRHAGIC SKIN MANIFESTATIONS ACCOMPANYING HEMOPHILUS INFLUENZAE MENINGITIS

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HEMORRHAGIC skin manifestations occurring during the course of *Hemophilus influenzae* meningitis are extremely rare. An extensive survey of the literature disclosed that only two such cases¹ have been previously reported; hence it was deemed of interest to report the following case.

CASE REPORT

R. C., a 6-year-old Negro boy, was admitted to the Children's Hospital Nov. 28, 1947, because of drowsiness, headache, and a rash on his abdomen. He had apparently been well until two days prior to admission when he developed a persistent frontal headache and vomited once. His mother ascribed this to constipation and administered a laxative and aspirin. The headache persisted, and during the morning of the day prior to admission he vomited two times, following which another laxative was given with poor returns. In the afternoon the mother noted that he cried out when touched or moved. Liniment was applied without relief. He refused all food that day and in the evening was unable to turn his head or bend his neck. Fever and mild delirium were noted at that time. He slept poorly during the night and on the morning of admission developed a "rash" on his abdomen and diplopia and became quite drowsy. There was no known exposure to contagion.

The past and family histories were irrelevant.

On admission to the hospital the temperature was 100.8° F., pulse 108, and respirations 25. The pupils reacted sluggishly to light, and no subconjunctival hemorrhages were noted. The fundi, ears, nose, and throat were clear, and the mucous membranes presented no hemorrhages. The lungs were clear to percussion and auscultation, and the heart revealed a sinus tachycardia with a rate of 108, P₂ greater than A₂, no enlargement and no murmurs. A few small, discrete, cervical and inguinal lymph nodes were palpable. The abdomen and genitalia were normal. A petechial rash was present over the abdomen, thorax, and upper extremities, no hemorrhages being noted on the palms, soles, lower extremities, or face. There was a marked stiffness of the neck, and the Kernig and Brudzinski tests were strongly positive. All deep tendon reflexes were hyperactive.

Spinal fluid obtained on admission was cloudy and was reported as follows: protein 600 mg. per 100 c.c., sugar 5 mg., and leucocytes 6,800, with polymorphonuclears 95 per cent. A rare gram-negative bacillus was found on direct smear, and from a culture, gram-negative pleomorphic bacilli morphologically and culturally resembling *H. influenzae* were obtained. Smear and culture of material aspirated from one of the petechiae showed gram-negative bacilli morphologically resembling *H. influenzae*. The blood culture grew *H. influenzae*. Following this report 50,000 units of streptomycin were instilled intrathecally, and 125 mg. of precipitable nitrogen anti-influenza Type B rabbit serum (with one gram of sulfadiazine) were given intravenously in 500 c.c. of 5 per cent glucose and Hartman's solution. Sodium sulfadiazine, one gram, was given orally every four hours with equal doses of sodium bicarbonate, and 200,000 units of streptomycin were injected intramuscularly every three hours.

The admission blood count was as follows: 9 Gm. per cent hemoglobin, 2.9 million red blood cells, and 9,000 leucocytes, with 85 per cent neutrophils.

¹From the Children's Hospital, and the Department of Pediatrics, George Washington University School of Medicine.

On the second hospital day 50,000 units of streptomycin were again instilled intrathecally, and the spinal fluid at that time contained protein 300 mg., sugar 45 mg. and 3,900 leucocytes, of which 90 per cent were polymorphonuclears. The sulfadiazine blood level was 13 mg. The intramuscular streptomycin was reduced to 150,000 units every three hours and the oral sulfadiazine increased to 1.5 Gm. every four hours. The patient appeared much improved clinically and answered questions readily. The petechiae on the anterior trunk had regressed, but a new crop had appeared on the back. A culture of the moderately injected pharynx revealed nonhemolytic *Staphylococcus albus* and *Neisseria catarrhalis*.

Again on the third hospital day additional petechiae were noted on the chest and arms. On this same day a profuse nosebleed occurred, lasting for one and one-half hours and stopping spontaneously. A blood count at that time showed 40,000 thrombocytes, 7.5 Gm. hemoglobin, 3.0 million erythrocytes, and 5,250 leucocytes, with 46 per cent neutrophils. The blood sulfadiazine level was 7 mg.; however, due to the low white blood cell count it was deemed inadvisable to increase the oral dose of sulfadiazine. Five hundred cubic centimeters of whole blood were given intravenously at that time.

Subsequent spinal taps performed on the fourth, sixth, eighth, and thirteenth hospital days revealed cell counts of 193, 120, 58, and 10, respectively, with a predominance of lymphocytes on the first three specimens. Fifty thousand units of streptomycin were instilled intrathecally at the time of each puncture. Culture of the spinal fluid obtained on the fifth and sixth hospital days revealed *H. influenzae*; no growth was obtained on the eighth and thirteenth hospital days.

The sulfadiazine blood level was maintained between 4 and 10.7 mg. from the third to the fourteenth hospital days, and no attempt to increase this dose was made because the white blood cell count varied from 3,400 to 6,500.

Another transfusion of 350 c.c. of whole blood was administered on the sixth hospital day after a moderately severe nosebleed occurred. At that time the hemoglobin was 7.5 Gm., and the red blood cell count was 2.4 million. Another transfusion was given on the eighth hospital day when the thrombocyte count was 98,000. After several days the red cell count and hemoglobin gradually returned to normal as did the thrombocyte count, and they remained so till the time of discharge. Spinal fluid examinations on the eighteenth and twenty-first hospital days revealed 20 and 10 cells, respectively, with normal sugar and protein content and negative smears and cultures.

Sulfadiazine was discontinued on the fourteenth hospital day and streptomycin stopped on the fifteenth hospital day.

During the first seven hospital days the temperature ranged from 99.2° to 100.8° F. (rectal), the pulse from 90 to 150, and the respirations from 20 to 30. From the seventh to the twenty-third hospital days the temperature ranged from 98° to 100° F. (rectal), the pulse from 80 to 100, and the respirations from 10 to 20.

Additional medication consisted of vitamins K and C and liver extract parenterally.

On the fourth hospital day a herpetic lesion developed at the right angle of the mouth, clearing readily by the eighth day with symptomatic therapy.

Additional laboratory findings revealed essentially negative urinalyses, a negative old tuberculin, a positive Schick, no sickling of the red blood cells in a twenty-four-hour smear, prothrombin time 93 per cent of normal, bleeding time 1 minute, 30 seconds, and coagulation time 3 minutes, 10 seconds. On the sixth hospital day the patient's serum failed to cause capsular swelling of the infectious organism.

The physical and neurological examinations were negative, as were the blood and spinal fluid on the twenty-third hospital day when the child was discharged. Two months after discharge a complete physical examination revealed no abnormalities.

DISCUSSION

This case of meningitis due to *H. influenzae* represents the first to be reported in which these organisms were isolated from a petechia and the third reported case of *H. influenzae* meningitis accompanied by hemorrhagic skin manifestations. There are also two more such cases of hemorrhagic skin phenomena associated with this type of meningitis in the files of the Children's Hospital (petechial smears were not obtained in either of those cases).

Although petechiae occurring during the course of *H. influenzae* meningitis are extremely rare, they do occur and might be expected to be even more frequent, inasmuch as a bacteremia and septicemia generally accompany this form of meningitis. The literature contains several reports of Waterhouse-Friderichsen syndrome^{1, 2} due to *H. influenzae* bacteremia and septicemia. The picture of bacteremia, septicemia, hemorrhagic manifestations, meningitis, and Waterhouse-Friderichsen syndrome due to *H. influenzae* is not unlike that due to meningococci, the over-all picture in both being merely the result of a fulminating bacteremia.

The case just reported is also of additional interest inasmuch as no residual neurological findings were noted despite the coexistence of a bacteremia, septicemia, and meningitis.

The repeated bleeding tendencies may be explained on the basis of capillary thromboses and hemorrhages due to the lodgment of *H. influenzae* and possibly to the thrombocytopenia.

SUMMARY

1. An extensive review of the literature and of the files of Children's Hospital disclosed five cases of hemorrhagic skin manifestations associated with meningitis due to *H. influenzae*.

2. In the case reported, *H. influenzae* was isolated from an aspirated petechia. Aspirations were not performed in the other four cases.

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COMPLETE ATRIOVENTRICULAR BLOCK ASSOCIATED WITH PATENT INTERVENTRICULAR SEPTUM

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COMPLETE heart block coexisting with congenital heart disease is rare. The lesion is uncommon, even in cases of interventricular septal defects, with which it is associated most frequently, according to the majority of authors. Since Von Stark, in 1903, first called attention to congenital complete atrioventricular block, some eighty to ninety cases have been reported in the literature. Wenner,¹¹ in 1944, classified eighty-five cases as being authentic instances of congenital complete heart block, while Crawford,³ summarizing the literature on the subject in 1947, recognized only about sixty. Crawford analyzed all cases of complete heart block in younger age groups and cited White's series of 10,000 cases at the Massachusetts General Hospital, in which the incidence of this lesion was 0.79 per cent. Again, seventy-two cases of complete atrioventricular block reported by Graybiel and White⁵ included only four cases of congenital heart disease and two cases of possible congenital heart disease.

Criteria for diagnosis of complete heart block in congenital heart disease consist of:

1. Symptoms or signs of congenital heart disease,
2. Bradycardia,
3. Electrocardiographic evidence of A-V block,
4. Negative history for infectious disease capable of producing complete heart block.

Atrioventricular block rarely may produce symptoms of palpitation or a disagreeable sensation in the chest or precordium in the adult. Usually, no symptoms at all occur in the presence of uncomplicated complete heart block; especially is this so in the infant.

CASE REPORT

An infant girl was examined at the age of 5 weeks because of the presence of a very loud cardiac murmur. It was systolic in time, maximal between the third and fourth left interspaces, blowing in character, moderate in pitch, of grade 6 intensity, and transmitted slightly toward the left. A thrill was palpable.

The pulse was full, irregular, and with a maximal rate of 62 per minute.

Ante-partum examination of the mother had revealed the slow fetal heart rate. Post-partum examination of the infant revealed no other developmental abnormalities. The patient was the second child (the sibling being age 3) and was delivered uneventfully by the normal route. The mother was Rh negative, the father, Rh positive.

At birth, the child weighed 7 pounds, 14 ounces, but was difficult to resuscitate. At 5 weeks she had gained up to 8 pounds, 2 ounces, and at 8 weeks, to 9 pounds, 9 ounces, with an over-all height of 23 inches. She slept fitfully and during the day was extremely restless and irritable. No cyanosis was present. Feeding became an early problem. At 17 weeks the mother first noted intermittent slight cyanosis, especially when the child was asleep. No other changes occurred throughout this time.

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A.



B.

Fig. 1.—A, Roentgenogram of 5-week-old infant showing ovoid-shaped cardiac silhouette. Electrocardiographic tracings illustrate complete atrioventricular block (see Fig. 2). B, Roentgenogram of same infant at the age of 5 months. Note especially increase in cardiac size

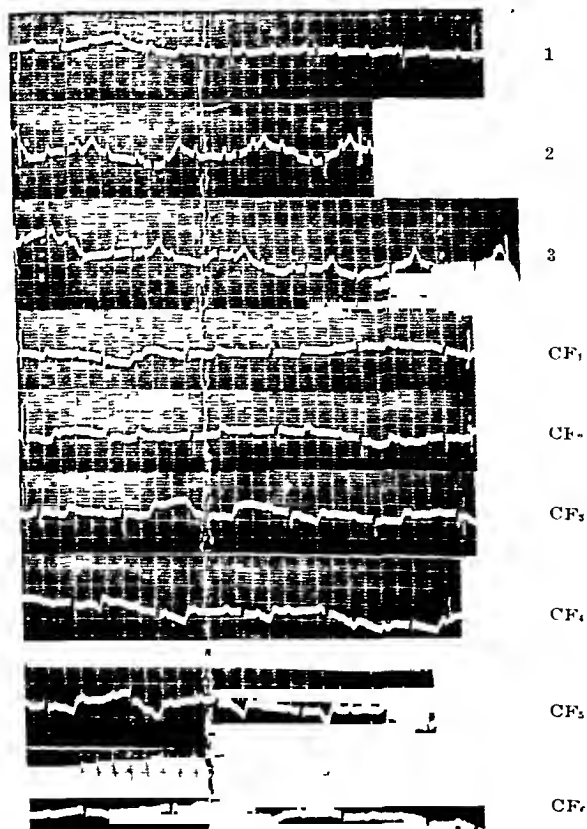


Fig. 2.—Electrocardiogram of 5-week-old infant, showing complete atrioventricular block

The heart rate on physical examination varied from time to time as follows:

May 26, 1947	50 per min.
June 18, 1947	60 per min.
July 16, 1947	42 per min.
Aug. 7, 1947	62 per min.
Aug. 22, 1947	60 per min.
Sept. 17, 1947	54 per min.

On x-ray examination, at the age of 5 weeks, the cardiac silhouette was seen to be obliquely ovoid, but did not present a pathognomonic configuration. By the end of five months, the heart shadow almost completely obliterated the left hemithorax with prominence especially of the left ventricle. (See Fig. 1.) Fluoroscopic examination confirmed the impression of generalized cardiac enlargement with emphasis on left ventricular enlargement.

Electrocardiographic tracings were obtained at the ages of 5 weeks (Fig. 2), 5 months, and 7 months, all showing complete atrioventricular block.

On the basis of the clinical evidence, it is felt that the diagnosis is made correctly of a complete atrioventricular block associated with patent inter-ventricular septum.

SUMMARY

A brief review of the literature on complete heart block coexisting with congenital heart disease is presented.

One case of complete atrioventricular block associated with patent inter-ventricular septum diagnosed by clinical methods is presented, in view of the rarity of this lesion.

I would like to thank Dr. H. P. Thomas, Chester County Hospital, West Chester, Pa., for his kindness in referring this case.

Photographs courtesy of Alden Thoroughgood, M/Sgt., and the Madigan General Hospital Clinical Photographic Laboratory.

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MANDIBULAR FRACTURES IN CHILDREN

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GENERALLY speaking, fractures of the mandible in children present considerably more of a problem than they do in adults. The length and shape of the crowns of the deciduous molars make intermaxillary wiring somewhat impractical, plus the fact that varying stages of root absorption are usually taking place. The 6-year molars and permanent incisors, when present, usually have incomplete root formation and are not favorable for either traction or anchorage. In very young children, any method which would require the jaws to be firmly fixed together would not be desirable for obvious reasons.

The literature gives us very little help in the handling of these cases. A very recent and complete 1,500 page work on oral surgery¹ carries exactly seven lines on mandibular fractures in children. An excellent book on traumatic surgery of the jaws,² which devotes ninety-seven pages to the discussion of fractures of the mandible, fails to mention this problem as specifically applied to children. A very comprehensive synopsis of traumatic injuries of the face and jaws³ also makes no mention of the problem. Peterson⁴ reports treatment of a fractured mandible on a 5-year-old boy by means of an arch bar and intermaxillary tie wires.

Skeletal fixation, which has proved to be of great value in certain types of cases, is definitely contraindicated due to the danger of inserting pins in the tooth buds of the permanent teeth, which are very close to the inferior border of the mandible. In uncomplicated cases without much displacement of the fragments, a head cap with an elastic bandage under the chin will sometimes provide enough stability and fixation. In place of the plaster head cap, which is very heavy and uncomfortable on children, the canvas aviator-type of helmet, which we have all seen small boys wearing, is very effective. The wide ace elastic bandage can be fastened to each ear tab with a safety pin and tightened up from time to time by the child's mother. Fortunately union takes place very rapidly in cases without infection.

In cases where there is wide separation of the fragments and considerable traction is going to be required to reduce the fracture, plus very firm fixation to keep the fragments in apposition, open reduction and direct bone wiring appears to be the most logical treatment. Such a case is presented herewith.

CASE REPORT

History.—On April 19, 1948, a 6-year-old white boy living on a farm in Mississippi was riding with his father on a tractor pulling a disc plow. He fell from the tractor, and the plow passed over him. He sustained a severe 18-inch laceration along the inner surface of his left leg and thigh, a 2-inch laceration along the lower border of the right side of the mandible exposing the bone, a fracture of the head of the left tibia, and a fracture of the right side of the mandible between the first permanent molar and the second deciduous molar.

First Aid Treatment.—He was taken to a nearby hospital, where he was given tetanus antitoxin and the wounds cleaned and closed. A rubber dam drain was left in the wound of the jaw.

Clinical Examination.—The patient was brought to St. Vincent's Hospital, Birmingham in a car and was first seen about noon on the day after he was injured. His general condition was only fair. He had slept very little the

previous night (even though he had been given sedation) and was exhausted from the long trip in the car. There was no evidence of any brain injury. The mandible was markedly displaced forward and to the left giving the clinical appearance of a dislocation. He could not close his mouth and had been drooling saliva to such an extent that he was quite dehydrated. His father stated that he had been unable to take any fluids by mouth since the injury. The temperature was 101.2° F., the pulse rate 130.



Fig. 1.—Fracture of right side of mandible of 6-year-old boy with wide separation of fragments. Note radiolucency of the V at the front of the posterior fragment and the corresponding radiolucency in the anterior fragment which indicate the inner cortex is on one fragment and the outer on the other. The permanent molar in the posterior fragment should be up against the deciduous molar in the anterior fragment. The developing cuspid and bicuspids can be seen in the anterior fragment and the developing 12-year-old molar in the posterior fragment.

Roentgenographic Examination.—The roentgenogram of the right side of the mandible (Fig. 1) revealed a complete fracture just anterior to the first permanent molar, which had not yet erupted. There was such a wide separation of the fragments, due to the left and forward displacement of the anterior one, that the condition might have been misinterpreted as the loss of a tooth together with some bone substance. Upon closer examination, however, the two deciduous molars were seen to be present in the anterior fragment and the first permanent molar and developing crown of the second permanent molar in the posterior fragment. The third molar is, of course, not present at this age.

The radiolucency of the V on the anterior border of the posterior fragment and that of the corresponding V on the anterior fragment indicated that the inner cortex was present on one and the outer on the other.

The roentgenogram of the left side of the mandible revealed no evidence of fracture.

Laboratory Examination.—R.B.C., 3,150,000; W.B.C., 11,000; differential, 77 polymorphonuclears, 18 lymphocytes, 5 large monocytes; hemoglobin, 57. Urine: negative.

Treatment.—The patient was given tetanus and gas gangrene antitoxin on admission and also 500 c.c. of 5 per cent glucose in normal saline, intravenously. Penicillin, 50,000 units every three hours, was started. He was given $\frac{1}{300}$ gr. of atropine at 3 P.M. and taken to the operating room at 4 P.M. for open reduction of his fractured mandible.



Fig. 2.—Postoperative roentgenogram showing perfect reduction and fixation with tantalum wire. The horizontal loop goes through a hole in the lower border of each fragment. The vertical loop goes through a hole in the center of the V in the posterior fragment and corresponding hole in the center of the V in the anterior fragment. The two ends of this loop have been twisted together under the lower border. The developing teeth have been carefully avoided. The vertical loop gives the appearance of being in the second bicuspid follicle, but this is caused by angulation as the hole is beneath it.

Operation.—Under ether anesthesia an incision was made beneath the lower border of the mandible which incorporated the original wound. The ends of the bone fragments were exposed and easily approximated after cleaning out the interposed soft tissue. Using the smallest drill available and drilling slowly to avoid heat, a hole was placed in the middle of the V on the posterior fragment and one in the corresponding spot in the anterior fragment so that when the fracture was reduced these holes coincided. As was thought from study of the roentgenogram, the hole in the posterior fragment had to go through only the outer cortex and that in the anterior fragment through the inner cortex. A piece of tantalum wire, 0.020 of an inch in diameter, was placed through these two holes and tightened under the lower border of the mandible. A hole was then drilled in the lower border of each fragment about one centimeter from the fracture line, extreme care being taken to get beneath the tooth buds of the developing bicusps. Another piece of 0.020 tantalum wire was placed through these holes and twisted together. The mandible was now very firm and stable. The anesthetist reported that the teeth now came together perfectly and also remarked on the improvement in the patient's respiration upon reduction of

the fracture. There was no evidence of bleeding into the mouth. The subcutaneous tissues were closed with 00 catgut and the skin with black silk. The immediate postoperative condition of the patient was good. He was given 500 c.c. of 5 per cent glucose in normal saline during the operation. A cast was applied to the left leg and a window made in the cast so that the soft tissue wound could be dressed.

Course.—The postoperative course was surprisingly smooth and uneventful. He was given $\frac{1}{4}$ gr. codeine by hypodermic injection upon return from the operating room. After reacting from the anesthetic he began to take fluids by mouth for the first time since injury. The temperature at 8 p.m. was 102.4° F. He had a very good night, and the temperature the following morning was 99.6° F. There was very little pain or swelling, and he could swallow freely. He was given 500 c.c. of whole blood and 500 c.c. of normal saline. Fluids were given freely by mouth. The postoperative roentgenogram (Fig. 2) showed the fragments to be in perfect position.

On the second postoperative day his temperature was 99.4° F. There was no pain and very little swelling of the jaw. Half of the skin sutures were removed.

On the third postoperative day he was returned home to be placed under the care of the referring physician. Before leaving the hospital he was given 300,000 units of Duraellin.* His temperature was normal, and his general condition was very good.

The remainder of the skin sutures were removed by his physician one week later, and he reported that the wound had healed perfectly with no evidence of drainage or infection. The patient was on a soft diet and the jaw functioning perfectly with no discomfort. Subsequent reports indicate that firm union has taken place with no evidence of tissue irritation from the tantalum wires.

SUMMARY

1. Fractures of the mandible in children present difficult and individual problems quite different from similar cases in adults.
2. The literature contains very little reference to these cases.
3. In complicated cases open reduction appears to be the method of choice, but extreme care must be exercised to avoid the permanent tooth buds.
4. Tantalum wire, as first reported by Burch and Carney^{5, 6} and later by Bellinger,⁷ causes less foreign body reaction than any other material that has been used thus far.

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*Made by Eli Lilly and Company, Indianapolis, Ind.

Medical Care

COMMON RESPIRATORY TRACT INFECTIONS IN INFANTS AND CHILDREN

DIAGNOSIS AND TREATMENT

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ALTHOUGH important advances have been made in our knowledge regarding certain of the respiratory diseases, the great majority of these common infections still defy accurate classification. Terms such as nasal pharyngitis, bronchitis, and "flu" are almost meaningless as applied to describe these infections. Applying such terms to respiratory tract infections is comparable to speaking of the inflammatory diseases of the meninges as spinal or cerebral meningitis. The intelligent management of the various forms of meningitis today requires an accurate etiologic diagnosis. Unfortunately, we do not as yet have many practical laboratory methods for the diagnosis of respiratory tract infections, but we do have a greatly improved understanding of the pathogenesis and etiology of these diseases. By approaching respiratory tract infections etiologically we should improve our ability to recognize them.

Infants and children who are being attacked for the first time offer an opportunity to study the clinical and pathologic features of these varied diseases in their relatively pure form. It seems important to conceive of the respiratory tree as a single unit which is capable of extremely varied reactions to infectious agents. These reactions may take various forms in the human subject, dependent upon age, immunologic, physiologic, and many other factors, such as dose, which serve to alter the picture. Different agents may produce a similar clinical picture and a single agent such as influenza A may simulate any stage of respiratory disease from latent or mild to extremely severe respiratory tract involvement. Dingle¹ has recently pointed out that the undifferentiated respiratory tract infections can be segregated "only by the exclusion of diseases of known cause, such as tuberculosis, diphtheria, beta hemolytic streptococcus infections, influenza, and psittacosis." Additional common diseases such as measles (rubeola), scarlet fever, and whooping cough might be added to this list.

The problem of the largest group of undifferentiated respiratory diseases still remains; and, as Dingle¹ states, they form a "clinical spectrum" extending from the common cold to atypical pneumonia. The Commission on Acute Respiratory Diseases has been able to separate four etiologic groups which clinically may fuse with one another, but still have different etiologic agents (most probably viruses) and certain definitive features when studied critically. The four categories which may represent separate etiologic entities are as follows:

1. The "common cold."
2. "Acute respiratory disease" (ARD).
3. Nonbacterial exudative pharyngitis and tonsillitis.
4. Primary atypical pneumonia.

Many previous workers²⁻⁵ have demonstrated that the coryzal type of cold with a one- to two-day incubation period could be transmitted to well human beings by bacteria-free filtrates, but the Commission on Acute Respiratory Diseases⁶ deserves the credit for delineating a second type of mild respiratory disease which is a separate and distinct entity most probably due to a virus. This disease they have chosen to call "acute respiratory disease" (ARD). It is distinguished by a five- to six-day incubation period, feverishness, chilliness, and headache. Sore throat is common but of rather mild degree in comparison to the patients who have exudate in the throat. This disease has been transmitted to human subjects by bacteria-free filtrates, and has been shown to be immunologically distinct from coryza-type colds. Rechallenge of subjects showed complete protection to this agent whereas no protection on rechallenge was demonstrated in subjects who had previously been infected with coryza-type filtrate. No cross immunity could be shown, which served further to define these agents as separate and distinct.

In infants and children the same "clinical spectrum" applies but may be more sharply defined in many instances. The first colds of normal full-term babies usually appear in the first few months as mild, almost afebrile coryzal-type infections, characterized by sneezing, cough, and "stuffed-up" noses. There may be mild anorexia. The physical findings are minimal and the white blood count is usually normal. Acute respiratory disease is difficult to delineate sharply in the present state of our knowledge but these more febrile responses are usually not seen until later in infancy when they may be associated with complications of a secondary character such as otitis media or cervical adenitis. Bacterial pneumonias also may frequently be associated with this illness. A separate and distinct entity is seen early in infancy which we have chosen to call "primary pneumonitis of infancy." Further details of this disease will be given briefly in a later part of this paper.

Nonbacterial exudative tonsillitis and pharyngitis is described by Dingle⁷ as "a mild disease of short duration. The onset is ordinarily gradual, and the early complaints of the majority of patients are those of feverishness, headache, and anorexia. Symptoms of sore throat, hoarseness, and cough, often productive, are noted by 75 per cent or more of the patients. . . . Nasal symptoms are not prominent." Moderate injection of the pharynx with gray or yellow pin-head exudate on swollen lymphoid follicles is seen on examination of these patients. This disease is rarely seen in the early months of infancy but makes its appearance at about one year of age, at which time it is usually featured by a severe illness with an acute onset, and high fever, sometimes ushered in by a convulsion. The findings are those of moderate swelling of the pharyngeal lymphoid tissues with a gray or whitish exudate which tends to remain discrete. The exudate may not appear for twelve to eighteen hours after the rather dramatic onset in many of these patients. The disease runs a self-limited course in three or four days and complications are rare.

Exudative tonsillitis and pharyngitis due to beta hemolytic streptococcus is also an acute disease in childhood and can frequently be differentiated from the nonbacterial group by the physical findings. The membrane is dirty gray

or yellowish and often confluent, there is more edema and redness, and usually an associated cervical adenitis. Throat cultures reveal large numbers of beta hemolytic streptococcus as the predominant organism. The white blood count is elevated as a rule with an increase in polymorphonuclear cells. The final proof of invasion in these patients is dependent upon a definite change in the antistreptolysin titer, but this test has very little practical value. It should be remembered that the majority of cases of exudative tonsillitis are not due to beta hemolytic streptococcus and the patients will recover spontaneously. Patients who are severely ill with this disease and have large numbers of these organisms in their cultures should be treated with penicillin.

Primary atypical pneumonia as seen in childhood varies very little from the adult disease, except that it may be milder in the usual case. Many children have no complaints except for cough and some anorexia. If a roentgenogram of the lungs is taken, one is frequently startled by the infiltration which is usually light and patchy in character but may be limited to a definite area.

The diagnosis involves ruling out other diseases such as tuberculosis, bacterial pneumonia, psittacosis, Q fever, and influenza. The cold hemagglutination test is helpful when it is positive, but a negative test does not rule out the disease.

In infancy, primary pneumonitis^{7,8} may occur as an epidemic disease involving groups of babies in an institution, or occasionally it is seen to occur sporadically.⁹ In the epidemics *all* stages of respiratory tract involvement occurred in the various patients in the same ward. Some of the babies manifested sneezing and cough *only*, others had marked cough with inspiratory dyspnea, while the majority were severely ill with attacks of cyanosis and marked dyspnea. In the sporadic cases which we have observed, the same symptom pattern of cough, dyspnea, and cyanosis has been manifested in the most acutely ill patients with pneumonitis. However, patients with mild cases with little or no evidence of lower respiratory tract infection have been seen. The age and maturity of the patient appear to be responsible in the main for the variations which are met. In the epidemics the morbidity and mortality have been extremely high in prematurely born babies as contrasted to normal full-term infants.

The onset of the illness in the baby is rather abrupt and at times the pulmonary symptoms may be the first observed. Sneezing and cough are the first symptoms in most of the patients. The temperature response is usually slight but may rise to 102° or 103° F. for a short time. There are few physical findings in the milder cases. The mucus in the pharynx is abundant, whitish, thick, and tenacious in character. Râles may be heard over the lung fields on careful examination. The roentgenogram of the lungs reveals diffuse shadows which are bronchial in distribution and usually widespread, but may be confined to a single lobe of the lung.

The diagnosis is made by the symptom pattern and by the rather characteristic shadows seen in the roentgenograms of the lungs. The white blood count is usually normal or only slightly elevated with an increase of lymphocytes.

Pharyngeal smears made from these patients in the acute stage of the disease reveal a great predominance of epithelial cells which contain typical cytoplasmic inclusion bodies. This finding is considered helpful in the diagnosis, particularly when the inclusion bodies occur in large numbers (10 to 20 per 100 cells) in patients who satisfy the other criteria of primary pneumonitis.

Many post-mortem studies have revealed a distinct pathologic picture in the lungs of infants dying from the epidemic form of this disease. The prominent features are destruction and proliferation of bronchial epithelium with peribronchial infiltration of mononuclear cells. Typical cytoplasmic inclusion bodies are found in the epithelial structures of the pulmonary tree. This includes the nasal, pharyngeal, tracheal, bronchial and alveolar tissues. Because of the probably ubiquity of this agent, the interpretation of the finding of inclusion bodies must be made with caution. The same point of view must be assumed as we now have regarding the beta hemolytic streptococcus. The finding of this organism in the nose or throat does not always mean that the patient is suffering from invasion by the coccus. Likewise the finding of inclusion bodies may or may not be significant. It seems to depend in the main on the correlation of this finding with clinical evidence of a characteristic disease, and whether they are found in large numbers exclusive of other findings in carefully prepared pharyngeal smear biopsies. The age of the patient probably plays a large role also in the occurrence of these bodies.

Influenza is an epidemic virus disease, highly communicable, which primarily affects the respiratory passages. Epidemics of influenza A are now established as occurring at fairly regular intervals of two or three years, usually beginning in the late fall or winter months. The last few epidemics of influenza B have occurred at approximately four-year intervals. It is important to recognize this fact as the diagnosis of influenza should probably not be made except during an epidemic. Its sporadic incidence is known to be rare.

In a study of an epidemic of influenza¹⁰ occurring in infants and children, the disease was characterized by high, irregular, and biphasic fever curves. Leucopenia was not found to be present. Acute pharyngitis, often hyperemic, and lassitude were the most prominent physical findings. None of the patients manifested severe laryngitis or croup.

Influenza A virus was isolated from throat washings taken from a number of the patients and inoculated intra-allantoically into developing chick embryos. The serologic diagnosis of the epidemic was established by the demonstration of significant increases in neutralizing antibodies by means of the hemagglutinin inhibition test. The neutralizing antibody response of infants, who in all probability were having their first infection with influenza A virus, was found to be of approximately the same magnitude as that of older children.

In the serums of five infants who experienced their first known attack of influenza A, antibody response as measured by the agglutination inhibition test was greatest to the strain of influenza virus isolated from the nasopharynx of one of the infants. Mean antibody levels attained were progressively lower to the PR8 and W.S. strains of influenza A virus and swine influenza virus, respectively, although some antibody was formed against all of the viruses tested.¹¹

The most characteristic clinicopathologic feature of epidemic influenza as seen in a recent proved epidemic was an acute pharyngitis.¹² The pharyngeal smears of over 300 young adults and children suffering from influenzal A infection were studied, as well as similar tissues from control groups during, and six months after the epidemic. Increased destruction of pharyngeal epithelial tissues was definite as compared with the control specimens. The single most important micropathologic feature of the pharyngeal exudate of these influenza patients was a mononuclear exudate, which is consistent with the pathologic findings in certain other types of virus infections, both in man and animals. In our study a polymorphonuclear exudate frequently presaged a complicating secondary bacterial infection.

TREATMENT

The intelligent management of the common respiratory tract diseases is dependent upon a reasonably accurate diagnosis. Inasmuch as the great majority of these infections can now be considered to be caused by nonbacterial agents, no specific drug therapy can be offered for the primary diseases. The occurrence of secondary or synergistic bacterial disease may offer a real indication for a specific drug, but our choice should be dependent on some accurate knowledge of the infecting organism.

In the patient with exudative tonsillitis and pharyngitis due to beta hemolytic streptococcus, full therapeutic doses of penicillin should be employed. In infants, we use doses of 50,000 to 100,000 units of aqueous penicillin given intramuscularly at twelve-hour intervals; sulfonamide drugs such as sulfadiazine are also effective and may be more practical and economical in the home treatment of patients. Doses of approximately one grain per pound of body weight are used in infants and small children, divided over the twenty-four hour day and given at four-hour intervals. Somewhat smaller doses are used in older children. A good intake of fluids should be encouraged when the patient is on sulfonamide drug therapy.

The most important consideration in the common respiratory tract infections should be directed toward prevention. Isolation of the premature and newborn infant is effective against these highly contagious diseases. Home life as opposed to institutional life is most desirable as a practical preventive measure. Most of the diseases are self-limited infections, and require no special measures over and above good hygiene and common sense, but complications are frequent and should be watched for and prevented whenever possible. It would appear to be a well-established fact that the common primary virus diseases are precursors of bacterial infections; thus, every effort should be employed which will aid in their prevention.

Congestion and irritation which lead to various degrees of pulmonary obstruction should not be underestimated as important factors leading to complications. Any means available for reducing the irritation, congestion, and obstruction should be helpful. Postural drainage has been used successfully, especially in infants where the passages are small and the infant may be physiologically unable to cope with the secretions and congestion caused by the primary infections. The upper as well as the lower pulmonary passages can be drained much

more effectively when infants and children are placed in the prone or abdominal position. Ineffective and troublesome cough is often markedly relieved by the use of posture alone. The cough is probably one of the body's most effective defense mechanisms and should not be suppressed unless it is beginning to interfere seriously with the patient's rest. The two primary diseases where some relief of cough is most indicated are measles (rubeola) and whooping cough (pertussis).

Aspiration or gravitation of infected exudate into the lung has been shown to be the main mechanism involved in the pathogenesis of bacterial pneumonia. In so far as posture may play a role in preventing aspiration or gravitation, it should be helpful in the prevention of this serious complication of common respiratory disease.

Specific polyvalent vaccines have been shown to be effective in the prevention of type-specific pneumococcal infections. Their use in civilian practice has not as yet become widespread.

Vaccination against influenza A and B is the only method now in practical use for the prevention of primary virus diseases of the respiratory tract. It is effective only against influenza A and B and probably has no prophylactic effect against other virus diseases. The reactions are relatively mild when the proper doses are used. Infants under 6 months of age need not be vaccinated. Up to 2 years of age, .25 c.c. of vaccine is given subcutaneously in one inoculation only. From 2 to 6 years of age 0.5 c.c. is recommended, and from 6 years on, one c.c. doses are well tolerated. The present vaccines should not be given to egg-sensitive children. One inoculation would appear to be about as effective as multiple injections, and is the most practical method for wide application.

In measles (rubeola) concentrated gamma globulin of human source is very effective in prevention of this disease if given after exposure. A good indication for prevention should be present, as this method provides passive protection for a short time only. The material is so effective that modification of the disease is difficult to be sure about if given before the onset of symptoms. Whether or not it will prevent measles encephalitis is not known.

The prevention or modification of whooping cough is possible when exposure is definite by the use of hyperimmune human serum. This substance plays a very useful role in the modification and therapy of infants suffering from whooping cough.

In summary, no known specific therapeutic agents are available for the treatment of the common viral respiratory tract infections. Penicillin, streptomycin, or sulfonamide drugs are useful in treating known bacterial infections when the organism is identified as a susceptible one. Postural drainage as an aid in preventing secondary bacterial disease is recommended, especially in infants and small children.

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Clinical Conference

CONFERENCE AT THE CHILDREN'S HOSPITAL OF MICHIGAN

DR. PAUL V. WOOLLEY, JR., PEDIATRICIAN-IN-CHIEF

Case 1. Methemoglobinemia Due to Well Water

DR. MARGARET DOWELL (Resident in Pediatrics).—This 18-day-old female baby was admitted on Feb. 17, 1948, because of cyanosis since the sixth day of life. She was born at a suburban hospital and apparently progressed well for five days, but soon after reaching home became blue and was returned to the hospital where she was kept in oxygen for five days before again being discharged. During the next few days she was said to have only intermittent attacks of cyanosis but on the day before admission she was irritable, passed several liquid stools, and required water between each feeding. During the day of admission the cyanosis reappeared and was more intense than ever before. It was learned during questioning of the parents that a sibling had been treated at this hospital three years ago for the same complaint, the cause of which was never determined.

Examination showed the baby to be husky but deeply cyanosed. The cyanosis was of the same intensity whether the infant was quiet or crying, in or out of oxygen. There was no cardiac enlargement or murmur, the lungs were clear and well aerated, and the liver was not enlarged. Both the pulse and respiratory rate were increased. Laboratory data, such as have been obtained, are of importance mainly in showing an initial hemoglobin concentration of 16 Gm. per cent, 7 Gm. of which was methemoglobin. Treatment on the day of admission was limited to the administration of 500 mg. of ascorbic acid intramuscularly and the repetition of this four hours later. A blood sample taken before the second injection showed a rise in oxyhemoglobin to 12 Gm. per cent and a determination the following morning revealed only 0.7 Gm. per cent of methemoglobin. The child at present appears entirely normal and happy, apparently none the worse for her experience.

DR. PAUL V. WOOLLEY, JR.—The resident staff is to be congratulated on its alertness with this case. The chart of the sibling was obtained, and when the diagnosis was found to have been methemoglobinemia of unknown etiology, treatment was immediately instituted for the present infant. Since attention lately has focused upon nitrates in well water as a common cause of methemoglobinemia, the parents were questioned concerning their habitat. They live rurally and obtain their drinking water from a shallow well; the same well was utilized when the other baby was sick. It is interesting, parenthetically, how often we stand on the brink of fame without falling or being pushed; the medical student who wrote the history on the first case devoted a complete paragraph to a description of the well and the salty taste of the water but followed the problem no farther.

Methemoglobinemia in general is not rare in pediatric practice and is usually associated with the ingestion, accidentally or therapeutically, of substances capable of serving as oxidizing agents. Recently we have shown instances where sulfadiazine, acetanilid, and Phenacetin have each been thought to be at fault. Formerly it was seen following cutaneous contamination with aniline and similar solvents then employed in shoe dyes and marking inks. It has even been suggested that the duskiness which characterizes certain instances of diarrhea in babies may be due to methemoglobinemia produced through the action of pyrocyanin, the pigment of *Pseudomonas aeruginosa*. The role of nitrates has been known for years since these salts were introduced early as opaque media in gastrointestinal roentgenoscopy as well as in the treatment of enteritis. The common colon bacillus is able to reduce nitrates to nitrites and these, on absorption, undergo further reduction and thus serve as oxidizing agents. Nitrates, it will be recalled, occur in high concentration in certain immature surface waters and in this area we have now seen instances of poisoning from two separated communities and, according to the State engineers, there are other zones where nitrate well water is a potential hazard.

Treatment is usually dramatic and the mortality is low since cyanosis ordinarily appears before a critical reduction in oxyhemoglobin occurs. Methylene blue was long the reducing agent of choice but is now difficult to obtain, so that ascorbic acid has come into favor as a more readily available antidote. It is possibly a little slower in action than the dye, but, as illustrated by this case, is quite reliable.

QUESTION.—What happens to the hemoglobin during these various changes?

DR. LEONARD APT (Fellow in Hematology):—The iron in hemoglobin is usually present in the ferrous state and as such will combine with oxygen to form oxyhemoglobin. When exposed to oxidizing agents, the iron passes to a ferric state and is no longer capable of combining with oxygen. When reducing agents are introduced, the ferrous form is again active and once more combines with oxygen. Laboratory methods are available for both quantitative and qualitative estimations of methemoglobin. Methemoglobin can be readily differentiated from the reduced hemoglobin such as is seen in the cyanosis of congenital heart disease, since the latter combines readily with oxygen in the absence of a reducing substance.

FINAL NOTE

This patient was discharged on the day he was presented and the family was instructed to use city water until a new source could be developed. A sample of their water showed 974 parts per million of nitrates as compared with a safe level not in excess of 30 parts per million.

Case 2. Ratbite Fever Due to *Streptobacillus Moniliformis*

DR. MARGARET DOWELL.—This 3-year-old white boy was admitted May 11, 1948, because of chills and fever of one week's duration. One day before the onset of symptoms he had told his mother of having been bitten on the finger by a rat and she had noted a small puncture wound in the area indicated. The chills had occurred each evening and the fever had been present during the night with

usually only a minor elevation during the day. For three days before admission he refused to leave his bed although the mother could not ascribe this to any definite evidence of pain. The finger which had been bitten remained, during this period, only mildly inflamed and was not sore.

Upon admission he appeared acutely ill and cried constantly. His temperature was 102° F., pulse 136, and respirations 42. Marked swelling was noted about the right ankle which was also quite tender, and a second area of swelling occupied the region of the metacarpal phalangeal joints of the right hand. The middle finger of the left hand, where the bite was said to have occurred, showed two tiny puncture marks and minimal swelling of the distal phalanx: the lymph nodes in the left axilla, however, were swollen but not tender. Neither the liver nor the spleen was palpable, and nothing out of the ordinary could be detected in the chest. Over the trunk his skin was peppered with excoriated papules typical of scabies, but on the legs a different eruption was prominent—red, macular for the most part, with a tendency on the feet to form papules. Laboratory data obtained initially included normal urinalysis, negative Mazzini and tuberculin tests, and a white blood cell count of 14,000 per cubic millimeter with a predominance of polymorphonuclear leucocytes.

Early treatment was limited to the use of aspirin for control of pain and during the first four days his condition did not change. The fever was irregular but reached 102° F. each day and dropped to subnormal at the early morning recordings. The joints remained swollen and tender but new involvement did not appear. Several blood cultures were obtained and on the fourth day penicillin was administered with immediate response; his temperature has remained under 100° F., the joint swelling is subsiding, and his rash has disappeared. Typical growth of *Streptobacillus moniliformis* was observed in the earliest culture flask after five days' incubation.

DR. WOOLLEY.—It was not realized for a number of years that ratbite fever is really two unrelated diseases, one, the classical form (sodoku) due to *Spirillum minus*, the other, septicemia with *S. moniliformis*. The separation of these syndromes is usually accomplished quite easily although the possibility of them existing concomitantly must be kept in mind. Some of the more important points of divergence are as follows:

(a) The onset of sodoku follows an incubation period of about two weeks, and a chaneroid exacerbation at the point of inoculation ushers in the clinical symptoms. The Haverhill (*Streptobacillus*) type does not have a clearcut incubation period but begins with fever a few hours or days after the bite. The point of inoculation in the latter disease may remain slightly inflamed from the start and I have never seen it resemble the chanere of sodoku.

(b) The course of sodoku is one of periodic elevation of temperature with two or more asymptomatic days between peaks. The bacterial form tends to a plateaued fever or to daily fluctuations. Joint involvement is part of the Haverhill variety but is rare or absent in spirillosis although muscle pains are not uncommon in the latter. A distinct macular rash is not unusual in the bacillary disease but evanescent blotches and blushes during fever are the typical manifestations of sodoku.

(c) Both diseases are characterized by mild leucocytosis, but positive reactions to precipitin tests, such as those of Kahn, Hinton, and Mazzini, are seen exclusively in sodoku. Moderate anemia is present in both as the infections persist.

(d) The diagnosis in Haverhill fever is made through the recovery of the streptobacillus from blood cultures; detection of the spirillum ordinarily requires injection of lymph node emulsion into animals, preferably guinea pigs.

Interestingly enough, both forms respond to penicillin. Arsenicals earlier gave satisfactory results. The prognosis in each is also excellent if treatment is instituted within a reasonable period. One little feature of streptobacillus infection is disturbing; that is the theoretic ease with which these patients can be confused on clinical grounds with the rheumatic fever-Still's disease group. Children are unreliable in giving information and many ratbites occur during sleep, so that it is quite possible to overlook the importance of a superficial cutaneous lesion. In areas such as ours, where rats are plentiful and their contacts with children frequent, we are most conscientious in obtaining blood cultures and utilizing therapeutic tests with penicillin. The same thing, I might add, applies to the possibility of confusing sodoku with congenital syphilis; we have had one baby admitted here as syphilitic because of fever, irritability, splenomegaly, and positive Mazzini test, who turned out to have ratbite fever.

DR. W. W. ZUELZER (Pathologist-in-Chief).—It remains a source of amazement that we are not more generally bothered by rat-borne diseases; I do not understand why Weil's disease is so rare in this hospital. It is important to remember that the Haverhill type of infection can be acquired without the bite of a rat. Outbreaks have been attributed to contaminated food and milk.

FINAL NOTE

Penicillin was stopped after seven days and the child has remained well.

Case 3. Congenital Obliteration of the Bile Ducts

DR. ROBERT W. McCAMMON (Resident in Pediatrics).—This child is 15 months of age and was first admitted March 30, 1948, because of jaundice present since the ninth day of life. He is the third child in an otherwise normal family and was born after a supposedly uneventful pregnancy. Both jaundice and clubbing of the fingers were noted on the ninth day and the former has been progressively more severe. His early life was uneventful except for occasional bouts of diarrhea, and he gained steadily in size and weight. By 6 months of age he could sit, but since then development has continued more slowly so that while he crept at 11 months he still could not stand. His abdomen had become increasingly large, stools had always been light in color, and his urine was always dark and staining.

Examination showed him to be surprisingly well-nourished, weighing 21 pounds, and measuring 31.5 inches. His skin was bright lemon-yellow in color, and his mucous membranes were pale and stained. The anterior fontanel was widely patent and marked craniotabes was present. The fingers were definitely clubbed but the nails were not as thickened as is usually seen in cyanotic babies; the fingers did not seem sensitive nor irritated. There was a loud systolic mur-

mur over the precordium but it was soft in character, unaccompanied by a thrill, and free from sharp accentuation at any one point. The liver edge was 8 cm. below the costal margin and felt hard and rough, but no gross irregularities could be made out. The spleen also was enlarged, hard, and regular in outline. Essential laboratory data included an icteric index of 90, biphasic van den Bergh test, serum bilirubin 10 mg. per cent, and urine urobilinogen positive at 1:20 dilution but negative 1:30. A microcytic hypochromic anemia with hemoglobin of 3.2 Gm. per cent probably accounted for the heart murmur. The cephalin flocculation test was positive, but there was no reduction of prothrombin activity. X-ray studies of the long bones showed generalized rarefaction and low-grade rickets. Treatment during this first admission was limited to transfusions before he was removed by the parents who desired time to consider surgery.

He was readmitted two weeks later but had developed a severe upper respiratory infection which was complicated by diarrhea. He has now been returned to condition where surgery can be undertaken. It is interesting to note that since his anemia has been corrected, his color has changed from lemon yellow to a greenish yellow.

DR. WOOLLEY.—We are presenting this case in order to make a few points needing emphasis. First of all, it must be understood that we have no absolute method for diagnosing congenital defects of the biliary tract. Certainly progressive jaundice, increasing hepatomegaly, and absence of bile from the stools is most suggestive, especially if these continue until about 3 months of age. Exploration alone frequently does not provide a true answer. You have seen recently an infant who underwent laparotomy and in whom normal components of the biliary tract could not be identified. When Dr. Zuelzer presented the case at Pathologic Conference, following death during an outbreak of diarrhea, he demonstrated normal biliary structures and a healing of hepatitis. Exploration with the removal and examination of tissue affords the nearest approach to absolute diagnosis in doubtful instances. The clinical laboratory, while most helpful in ruling out certain confusable entities, does not possess a critical test in this condition.

Of the last dozen cases in which obliteration has been strongly suspected, the diagnosis has been confirmed on only three occasions. The remainder, on the basis of biopsy studies and/or clinical course, have been relegated to the heterogeneous and poorly understood groups labelled hepatitis and cholangiolitis. This is surprising since Ladd¹ in his definitive contribution mentions icterus neonatorum, erythroblastosis, hemolysis due to sepsis, and syphilis as the only important differential worries. He does place great stress upon the role of inspissated bile in the ducts and possibly this is the point of confusion: is the bile inspissated and the larger passages empty because of dysfunction secondary to hepatitis or ascending infection, or does the inspissation per se cause the liver changes? This point deserves re-evaluation, especially when we remember that we are but a few years out of the catarrhal jaundice-mucous plug era; knowledge of hepatitis as an epidemic and infectious disease, and of homologous serum jaundice are mainly outgrowths of the recent war. Three of our recent "obliterations" have cleared up spontaneously before surgery could be performed and each gave a

history of progressive jaundice almost from birth, persisting for from six weeks to two months. The prognosis, so far as the present patient is concerned, is not good. I have little doubt from our findings and the history that he has an anomaly, and probably less than one in five of these are theoretically amenable to surgery. We have had only one cure in recent years, a girl shown in this clinic some months back who had a usable outpouching of duet which was successfully anastomosed to the duodenum. She is now quite normal in all respects.

I believe we can conclude that we must be chary in reaching a diagnosis of congenital atresia of the biliary tract and depend upon a history of progressive jaundice for at least three months, increasing hepatomegaly during the same period, and exploration with the examination of biopsy material. This is agreeable to the surgeons since they feel that the parts are better delineated by then and that permanent damage is not done the liver through reasonable delay. It is hardly necessary to stress that much more knowledge of liver disease in infancy would be highly desirable. Dr. Rosenzweig, what can you say about the clubbing?

DR. SAUL ROSENZWEIG (Senior Cardiologist).—Pediatricians associate clubbing with the cyanotic cardias but it is important to remember that it also appears in pulmonary disease and in liver dysfunctions associated with jaundice. I do not recall having seen it develop in a baby only 9 days of age.

QUESTION.—Would punch or needle biopsies assist in diagnosis?

DR. WOOLLEY.—These have been used rather extensively elsewhere but we feel much information is gained by laparotomy since the surgeon and pathologist can observe the organ grossly and choose representative areas for biopsy.

FINAL NOTE

This child was explored the following day. A rudimentary gall bladder and cystic duet were found but there was no trace of either common or hepatic ducts. The child is still living two months later, but we obviously have little to offer him.

Case 4. Meningitis Due to Hemophilus Influenzae

DR. RUDOLPH M. JARVI (Assistant Resident in Pediatrics).—This 1-year-old child entered the hospital May 26, 1948, because of fever for ten days and a convulsion shortly before arrival. He had always been well and had developed normally. He had been irritable when his fever was first noted, had seemed to have pain in one ear, and had vomited once. He was examined by a physician who prescribed conservative doses of sulfadiazine after finding an acute otitis media. During the next four days his temperature fell gradually and his other symptoms disappeared, so that for two days he seemed quite well and the sulfadiazine was discontinued. During the four days prior to admission, however, he appeared lethargic and listless although he was apparently not febrile. On the day of admission the mother said he felt warm, vomited, and had a generalized clonic convulsion.

His convulsion had stopped when he reached the hospital and he was listless and stuporous. His eyes were fixed and no attention was given his surroundings. The right cardiac dull but not inflamed and the left appeared normal.

His throat was injected and although his neck and back were not rigid he resisted extreme flexion. There was nothing unusual in the examination of the chest or heart; his pulse rate was 120 per minute with a temperature of 101° F. Reflexes were generally hypoaactive and in keeping with his postconvulsive state. The laboratory data included normal urinalysis, white blood cell count elevated to 21,000 with a slight increase in the polymorphonuclear forms, a negative serology, and a negative reaction to tuberculin. Fluid obtained from a lumbar puncture was clear and under normal pressure but contained 128 white cells, of which 88 per cent were monoeytic, and the protein was elevated to 102 mg. per cent. Sugar was present in the usual amount and no organisms were detected in stained preparations. X-ray films of the mastoids were interpreted by Dr. Evans as showing, "low-grade inflammatory reaction of some duration," and films of the chest revealed well-aerated lung tissue.

A convulsive episode in response to upper respiratory infection seemed the best possibility on admission, especially since examination after the child recovered from his postconvulsive state still showed nothing pointing elsewhere. He was given both sulfadiazine and penicillin and later in the day sat up and took fluids eagerly. When the findings in the cerebrospinal fluid were recorded it was obvious that the initial impression was erroneous and attention was then focussed upon the possibility of an extradural process secondary to otitic infection; we still did not consider seriously a purulent meningitis. He slept well that night and on the following day sat in a high chair, smiled, and played. His temperature, however, remained elevated, and more cerebrospinal fluid was obtained. This contained 62 cells per cubic millimeter and again an elevated protein with normal sugar content. He was seen by an otorhinolaryngologist, who discounted the importance of any ear infection. There was no essential change in his condition during the next two hospital days except that the nurses felt, toward the end of this period, that he was a little more drowsy and irritable. His temperature remained elevated and tended to rise to higher levels than at admission. It was then that a report on the culture made from the second tap was obtained and showed group B, *Hemophilus influenzae*. Another lumbar puncture was done and by now the fluid was cloudy and contained over 400 cells with a predominance of polymorphonuclear forms; on the following day this had risen to 900 and the polymorphonuclear cells comprised 85 per cent. Treatment was changed by increasing the sulfadiazine, instituting streptomycin, omitting penicillin, and administering specific rabbit antibody. Today he is but slightly febrile and appears, as you can see, comfortable and free from obvious neurologic signs.

DR. WOOLLEY.—Contrary to the findings in older children and adults, infants often show little physically upon which to make a diagnosis of meningitis; with some, as in this instance, even in retrospect it is difficult to point out when the central involvement took place and how it should have been detected. It is a rule in the emergency room here that no child be sent home after a "febrile" convulsion until a complete examination of the cerebrospinal fluid has been made; a convulsion associated with irritability and drowsiness is the most common history obtained in early influenza bacillus meningitis. Physically these infants often seem normal and apparently do not experience any great discomfort

nor exhibit classic signs of meningeal irritation; this, in our experience, is especially true of those in the age where the fontanel is open and the skull bones are not rigidly fixed. With the universal use of chemotherapy for all the ills of childhood, the problem has become even more exasperating since suboptimal amounts of the drugs will often hold progression in abeyance without effecting a cure. I believe it logical to consider seriously the possibility of an otitic spread after the initial fluid was examined although we usually can detect some localizing signs with a juxtadural process. We would be inclined now to discount the importance of the ears since Pfeiffer's bacillus more commonly involves that area as an extension of the mucous membrane infection and independent of the spread to the bloodstream with subsequent meningeal localization.

QUESTION.—How long will streptomycin be continued?

DR. WOOLLEY.—Our plan of treatment for influenza meningitis over the past two years has included sulfadiazine in amount sufficient to provide a blood level between 20 and 30 mg. per cent for at least seven days after cultures are sterile, antiserum early in the course, repeated if the power to "quell" is lost, and streptomycin for three days only. As you know, we use no intrathecal therapy except in the rare case where organisms persist for over three days and yet are biologically sensitive to one of the treatment agents. I do not recall resorting to this in the *H. influenzae* group but we have found it advisable to use intrathecal penicillin in one or two pneumococcal patients out of some twenty babies treated. We also use more antibody than is customary in most places since so many of our patients are seen late and since previous sulfadiazine therapy confuses our appraisal of the severity of infection. Streptomycin, in our experience, has not altered dramatically the outlook for influenza meningitis, so that we use it only in conjunction with the tried and true remedies, sulfadiazine and rabbit antibody. Dr. Zuelzer can speak with feeling on the brain damage which takes place with each succeeding day of infection and it therefore is our aim in all types of meningitis to strike with all our armament rather than testing clinically the efficacy of single therapeutic agents; this holds especially for the Pfeiffer bacillus where differences in individual susceptibility are strain characteristics. I would also like to point out that we treat purulent meningitis in infants as if due to *H. influenzae* until proved otherwise. This is based on two concepts: first, that the influenza bacillus is more likely to be hard to demonstrate than the gram-positive cocci or the colon group; and second, that the treatment, as outlined, is adequate for meningitis due to the meningococcus, whereas smaller doses of sulfadiazine and penicillin, as commonly effective in the meningococcal form, are of doubtful value in the influenzal type.

FINAL NOTE

This child made an uneventful recovery following the treatment as outlined and was discharged eleven days after presentation. He was seen a month later in the clinic and was continuing merrily along the curve of normal development.

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The Social Aspects of Medicine

FIRST ASSEMBLY OF THE WORLD HEALTH ORGANIZATION

During the last week of June and the early part of July, 1948, the First Assembly of the World Health Organization was held in Geneva. Some 450 delegates from sixty-nine nations were present to discuss and act on the agenda prepared by the Interim Commission. At the meeting, Dr. Andrija Stampar, rector of the University of Zagreb, Yugoslavia, was elected president, and Dr. Brock Chisholm, head of the Canadian Army's medical service during the war, director general.

Priority was given to the programs for malaria, tuberculosis, maternal and child health, venereal disease, and nutrition. Dr. Stampar is reported as holding the viewpoint that WHO should be primarily a clearing house for health information and a source of technical help in times of need, rather than a super health department above the health departments of the individual nations.

Parts of recommendations which were acted upon are of interest to pediatricians, particularly those relating to child and maternal health. The following is quoted from "Official Records of the World Health Organization, No. 10."

MATERNAL AND CHILD HEALTH

An international programme for maternal and child health is recommended in view of the high incidence of preventable deaths among infants and mothers in large areas of the world; the effectiveness of available techniques in reducing mortality and improving the health of infants and mothers; the immediate and continuing need, for the protection of coming generations, of scientific guidance in the utilization of available foodstuffs; the high incidence of communicable and other preventable diseases among children; the widespread mental and emotional maladjustment and insecurity among children and youth; the insufficient understanding and knowledge among parents and others of the causes of ill-health and abnormal behavior of children; and the effects of economic and social changes on the physical, mental and emotional development of children.

Objectives.—

To assist governments in developing services and facilities that will assure adequate maternity care, the best possible chance of survival to infants, and to all children normal physical growth and development, mental and emotional health, and freedom from preventable disease; to pool knowledge, acquire new facts, develop standards of care, and distribute information in respect of all relevant matters; and to cooperate with other agencies on joint undertakings which apply knowledge and techniques in the fields of social and biological sciences and of education to problems of maternity and childhood.

Programme.—

Studies on:

Statistical and other research projects on the causes and methods of reducing maternal, infant and childhood morbidity and mortality

Child guidance and mental health of children
 Social aspects of a maternal and child health programme
 Facilities and personnel for providing maternity care and health services for children, including hospital and auxiliary services.

Assistance to governments.—Provision of:

Expert advice on administration of maternal and child health programmes
 Fellowships and visiting experts
 Experts or teams to demonstrate special services.

Action on the international plane.—

A programme of co-operation and joint action with organizations concerned with maternal and child health

Collection and distribution of relevant information, including:

Results of research and investigations

Information on current procedures, methods and administrative practices

Preparation of reports on maternity and child care, including standard techniques, methods and practices, and materials for use in health education programmes.

Organization.—

A section on maternal and child health as part of the WHO Secretariat

An expert advisory committee consisting of not more than ten members, meeting say twice a year

A panel of corresponding members

Individual experts and teams, employed on a temporary basis as required.

Another matter of pediatric interest relates to international standards of biological products which is quoted as follows:

INTERNATIONAL STANDARDS

Therapeutic, Prophylactic and Diagnostic Agents.—

Biological standardization is a heritage from the Health Organization of the League of Nations, under whose auspices international standards and units have been established for thirty-nine substances which are assayed by biological methods. By agreement with the Danish Government and with the British Medical Research Council, the State Serum Institute, Copenhagen, and the National Institute for Medical Research, Hampstead, serve as centres for the preparation, maintenance and distribution of international standards.

Objectives.—To provide the medical practitioner with biological products of proved efficacy; to supply health authorities with standards for measuring the value of the biological remedies placed on the market; to simplify the task of the manufacturers who need to express the potency of export products only in terms of accepted international units.

It is proposed to develop a reference service library which will probably include the transfer of the library of the Office International d'Hygiène Publique, and of the medical and health sections of the former League of Nations Library. An expert library staff will be developed to meet requests made by national health administrations and health experts for bibliographic material.

An important question is the relationship of nongovernmental health organizations, which, for example, in the United States play such an important part in the national health field. The importance of such agencies is recognized.

but WHO is an organization of governmental agencies and is supported by government contributions. The following is the statement of principles as regard nongovernmental agencies:

STATEMENT OF PRINCIPLES

Criteria to be applied in placing Organizations on the List of Non-governmental Organizations eligible to be brought into Relationship with WHO under Article 71 of the Constitution.

The WHO should, in relation to non-governmental organizations, act in conformity with any relevant resolutions of the General Assembly of the United Nations, and the following criteria should be met before an organization can be regarded as eligible to be brought into relationship:

(i) The organization shall be concerned with matters falling within the competence of the World Health Organization.

(ii) The aims and purposes of the organization shall be in conformity with the spirit, purposes and principles of the Constitution of the World Health Organization.

(iii) The organization shall be of recognized standing and shall represent a substantial proportion of the persons organized for the purpose of participating in the particular field of interest in which it operates. To meet this requirement, a group of organizations may form a joint committee or other body authorized to act for the group as a whole.

(iv) The organization shall have authority to speak for its members through its authorized representatives; evidence of this authority shall be presented if requested.

(v) The organization shall normally be international in its structure, with members who exercise voting rights in relation to its policies or action.

(vi) Save in exceptional cases, a national organization which is affiliated to an international non-governmental organization covering the same subject on an international basis shall present its views through its government or through the international non-governmental organization to which it is affiliated. A national organization may, however, be included in the list, after consultation with the Member State concerned, if the activities of the organization are not covered by any international organization or if it offers experience upon which the World Health Organization wishes to draw.

Comments on Current Literature

THE TREATMENT OF HAVERHILL FEVER

IT IS now fairly well established that fever following ratbite may be caused by either of two etiologic agents: *Spirillum minus* or *Streptobacillus moniliformis*. These two organisms, so different biologically, produce similar clinical pictures. The disease due to *Spirillum minus* is produced only by the bite of a rat or some other animal carrying the organism. On the other hand, septicemia due to *Streptobacillus moniliformis* results from ratbite, or may follow the ingestion of contaminated material.

Knowledge of *Streptobacillus moniliformis* dates from 1914 when Schottmüller, investigating a case of fever following ratbite, isolated from blood cultures an organism which he termed *Streptothrix muris ratti*. Within the next decade a similar organism was recovered in several instances from the blood of patients during febrile course following ratbite. In 1925 Levaditi, Nicolau, and Poineloux¹ named the organism *Streptobacillus moniliformis*.

The disease is characterized by abrupt onset with chills, fever, vomiting, and headache, following an average incubation period of about six days. There is characteristically an early maculopapular rash, frequently resembling that of rubella, and present mainly on the extremities. Arthritis, which is typically present, may be severe and may involve many joints. A characteristic fever curve has been described, rising abruptly at first with remission in from two to five days, followed by recurrence with arthritic symptoms. The white blood cell count may be normal, but as a rule is elevated.

In January, 1926, an epidemic of unusual fever occurred in Haverhill, Mass. Place, Sutton, and Willner² (1926) described the clinical findings and later in the same year the bacteriology of this epidemic was reported in detail by Parker and Hudson.³ Clinical findings corresponded well with those reported following ratbite; but none of these cases was associated with ratbite. From blood and joint fluid of some of these patients Parker and Hudson recovered a highly pleomorphic organism which proved to be gram-negative, and required serum for its growth in artificial medium. The source of the epidemic was traced to a dairy distributing unpasteurized milk. Believing this to be a new disease and a newly identified organism, these investigators termed the disease Haverhill fever (erythema arthriticum epidemicum) and the organism, *Haverhillia multiformis*. It is now felt that these organisms, reported independently, are the same. Cultured with a fair degree of ease from blood or joint fluid, the organism is described as a slender, gram-negative, non-acid-resisting rod which is highly pleomorphic and stains with difficulty. Irregularity of form is characteristic: swellings and enlargements; tendencies to form threads and toward branching. Fermentation of some carbohydrates occurs, and in general the organism requires blood or ascitic fluid for growth.

While the diagnosis of Haverhill fever is not especially difficult, therapy has presented a difficult problem. Until penicillin became available, no form of therapy seemed to be effective. This is in contrast to the excellent results arsenicals is favorable. In the case of *Streptobacillus moniliformis*, gold salt in experimental infection in mice, but its use in the treatment of infections in human subjects did not give dramatic response.

Since the introduction of penicillin, successful treatment by its use has been reported in a number of cases. Certain patients, however, particularly those with chronic infections and long-standing joint involvement, fail to respond to penicillin.

A recent issue (June, 1948) of the *Proceedings of the Society for Experimental Biology and Medicine* carries an interesting report by Jennie S. Levey and Stanley Levey.⁴ In an attempt to obtain information concerning the efficacy of various therapeutic agents, these investigators undertook a study of experimental infection of mice with *Streptobacillus moniliformis*. Evaluation of therapeutic agents was made by allowing inoculated mice to develop swollen joints before attempting therapy. The organism used was the Manning strain of *Streptobacillus moniliformis* isolated from the blood of a patient who developed severe arthritis. This strain proved extremely virulent for mice, swollen joints resulting as early as forty-eight hours following inoculation, and many mice succumbing at this time. Routine broth cultures were followed simultaneously with each group of inoculated mice. The agents tested were penicillin G, streptomycin, Myochrysine (gold sodium thiomalate), Solganal B (gold thio-glucose in oil), sulfathiazole, para-aminosalicylic acid, para-aminobenzoic acid, Promizole, Promin and methylene blue. Therapy was initiated three days after the first appearance of joint swelling. Evaluation of therapy was based on complete disappearance grossly of all joint involvement. The results of these studies, summarized by the authors in the following table, are of considerable interest.

TABLE I. EFFECT OF VARIOUS AGENTS UPON JOINT INVOLVEMENT PRODUCED BY *STREPTOBACILLUS MONILIFORMIS*

GROUP	DRUG	COURSE OF THERAPY	NO. OF ANI-MALS TESTED	NO. OF ANI-MALS CURED	PER CENT CURED
1	Control		63	1	1.6
2	Penicillin G	10,000 units I.P. 3x daily, 4 days	32	12	37.5
		1,000 units I.P. 3x daily, 6 days	16	11	69.0
3	Streptomycin	5,000 units I.P. 3x daily, 3 days	7	6	85.0
		2,500 units I.P. 3x daily, 3 days	17	13	76.0
4	Myochrysine	1.25 mg. I.V. every other day, 10 doses	17	0	0
		5 mg. I.P. single dose	5	0	0
		4.0 mg. I.V. every other day, 10 doses	8	0	0
5	Solganal-B in oil	10 mg. I.M. single dose	7	0	0
6	Sulfathiazole	1 % in diet, 38 days	11	0	0
7	p-Aminosalicylic acid	.5% in diet, 9 days	13	0	0
8	p-Aminobenzoic acid	.4% in diet, 21 days	10	0	0
9	Promizole	.5% in diet, 5 days	13	1(?)	0
10	Methylene blue	.2% in diet, 20 days	5	0	0
11	Promin	.5% in diet, 21 days	22	0	0

Of sixty-three controls, only one survived; penicillin G proved effective in 37½ per cent in one group of mice and in 69 per cent in another group; streptomycin proved more effective than penicillin for this strain of the organism, 76 per cent in one group and 85 per cent in another. Remission of joint involvement was more prompt in the streptomycin-treated mice. In a discussion of their results, Levey and Levey refer to a report by Sprecher and Copeland² in 1947. This is a case report on a patient with severe joint manifestations who was treated with penicillin for six days without remission, but who showed dramatic improvement following the third dose of streptomycin. Sprecher and Copeland suggest that variability in strain susceptibility may be an important factor involved.

The experimental study by Levey and Levey seems to bear out the general clinical impression that penicillin is effective in combatting infections with

Streptobacillus moniliformis but to a lesser degree than streptomycin. However, with the idea of strain diversity in mind, as well as drug toxicity, it is suggested that a combination of the two forms of therapy might yield the most satisfactory clinical results.

Evaluation of the newer antibiotics in the therapy of Haverhill fever must await experimental studies and adequate clinical trial.

RUSSELL J. BLATTNER.

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News and Notes

*Preliminary plans are being made for the next International Pediatric Congress which will be held at Zurich, Switzerland, in August, 1950.

Dr. Leonard Davidson has been appointed Professor of Pediatrics and head of the Department at the University of Louisville Medical School. Dr. James W. Bruce has been appointed Clinical Professor of Pediatrics.

Correspondence

London, England
July 12, 1948

The Meeting of the British Paediatric Association took place this year at Windermere on April 16, and it was with the greatest pleasure that we welcomed Dr. Henry Helmholtz, a Corresponding Member of our Association, who had been invited to deliver the first Windermere Lecture. This is a specially endowed lectureship, and Dr. Helmholtz chose as his subject "Milk, a European Child Health Problem." The lecture, which was excellent, will be published in due course. All of us were delighted to have him with us, and those who had attended the International Paediatric Congress in New York last July were especially pleased that Dr. Helmholtz, who was President of the Congress, was able to attend our meeting. We recalled the hospitality that had been accorded to us in the United States and the generosity of the American Committee that had made the trip possible for many of us, and we were all most happy to do what we could in this country for our distinguished visitor. The meeting had a record attendance, but as the proceedings will be published shortly, no further details are called for here.

During the past twelve months the most important events, affecting paediatricians as well as all other members of the medical profession, have been concerned with the proposed National Health Service, which actually came into effect on July 5 of this year.

As I am sure that this whole affair has received very full attention in American medical journals already, I do not propose to go into any details, but I must refer to certain salient points of this very important matter. In my last letter I commented upon what appeared to be a split in the profession over the National Health Service Act, arising from a divergent point of view between the general practitioner and his interests on the one hand, and the consultant and specialist, whose work is so largely bound up with hospital work and the teaching of medicine, on the other. Most of us felt, however, that a unified professional front was vital, and in the course of arguments and meetings in connection with this Act, it happily emerged that despite some difference in professional interests, the over-riding principle of professional freedom was all that really mattered, and that the consultants would, therefore, stand in with their general practitioner colleagues and support them in opposition to the Act as originally laid down. In view of all the circumstances, the British Medical Association decided to hold a plebiscite in February of this year so as to determine the position taken up by the profession as a whole on this vital issue.

The results of this plebiscite were very striking. There was an 84 per cent poll of the whole medical profession in Britain. Of those voting (38,534), 90 per cent expressed disapproval of the Act as it then stood; of 17,626 general practitioners (out of a total of 19,345 voting) who expressed disapproval, 17,037 also voted against accepting service. Of the consultants and specialists there were nearly 10 to 1 against. One of the most surprising things was the result of the voting of those who were themselves engaged in whole-time government service: of these, 634 disapproved and only 127 expressed their approval of the Act.

Such figures make it quite clear how strong was the feeling against the Act as it then stood. The Minister of Health was made aware by these figures of the strength of the opposition, and he was also given to understand that it was a fear of the introduction of a whole-time salaried service that was a chief cause of widespread apprehension and opposition.

On April 7, 1948, the Minister stated in the House of Commons that he was prepared to introduce an Amending Act whereby it would be made impossible for him to introduce a whole-time, state-salaried service except by further direct Act of Parliament, that he would explicitly allow complete freedom of publication even in criticism of the service by those engaged in it, and he also undertook to modify the basic salary in such a way as to meet the views of the general practitioner.

These concessions were of such an order as to alter the picture in a very material way, for they went very far toward assuring that professional freedom which we were so determined to preserve. Following the Minister's announcement the British Medical Association felt, very properly in view of the February plebiscite, that another vote should be taken in the light of the fresh position which had thus been created. This second plebiscite was held in April, and 40,622 medical men and women out of a total of 54,724 voted. Of these, 25,842 still expressed disapproval of the Act, but in view of the concessions offered by the Minister, the numbers in favour of accepting service and of trying to make a success of it was now almost equal to those opposed to entering the Service, and among these opponents there were only 9,588 general practitioners as compared with more than 17,000 who adopted such an attitude in the February plebiscite.

Quite clearly, in view of this swing-over of opinion, there no longer existed a strong united opposition to the Act, and the Council of the British Medical Association accordingly advised the profession to accept service under the Act as it will be amended.

There is general relief that a head-on collision has been avoided, and that following what was undoubtedly a great victory for the profession, concessions on both sides opened up the way to cooperation.

Further confirmation of the improved nutrition of children over here comes in the second study of the teeth of young school children, carried out by May Mellanby and Helen Coumoulos. It shows that the dental health of 5-year-old school children examined in 1943 was much better than that of the 1929 group, and that there was a still further appreciable improvement in 1945; a point of special significance is that the percentage of carious teeth showing arrest of the disease was almost twice as large in 1945 as in 1943. It is suggested that this state of affairs was due to the increased calcifying properties of the dietary of this country.

In March the Prime Minister announced that the Government had accepted the recommendations of the Curtis and Clyde Committees, and that a single central department concentrated in the Home Office should be made responsible for providing a home background for children deprived of a normal home life. The primary function of the Children's Branch of the Home Office would be to ensure that everything possible is done to give homeless children not only material care, but also the sense of security and status that the normal home provides. This is one of the most important and outstanding advances of a social paediatric nature that has come to pass in recent years.

During the last year we have suffered here from the most severe epidemic of acute anterior poliomyelitis ever experienced in this country. The corrected notifications of cases will probably total about 7,500, giving an attack rate of 3.8 per 100,000 population. One of the striking features was the higher age incidence of the patients, 34.9 per cent being aged 15 years and over. The mortality increased with age, from a minimum of 3.2 per cent at the ages of 1 to 4 years up to 34.7 per cent in persons aged 45 years and over. As shown in an important contribution by Ritchie Russell, physical activity in the preparalytic stage was definitely related to an increased severity of the subsequent paralyses.

(Signed) K. H. TALLERMAN.

Book Reviews

An Account of the Weather and Diseases of South Carolina. Lionel Chalmers, M.D., London, 1776.

This small booklet is made up of extracts from the writings of Dr. Lionel Chalmers of Charles-Town, S. C., which were published in 1776 in two volumes under the above title. Some fifty-odd of the 446 pages of the original text were concerned with pediatric subjects. These have been selected for reproduction by Dr. Joseph I. Waring, and reprinted in a small brochure by Mead Johnson & Company as a souvenir of the Centennial of the South Carolina Medical Association which was held in March, 1948. Dr. Waring contributes a short biography of Dr. Chalmers, who was born in Scotland in 1715, and came to Charleston in 1735, where he practiced until his death in 1777.

It is interesting historically, as it gives an excellent picture of the ideas held 200 years ago as to the causation of disease and the methods of treatment at that time. Included are discussions of such subjects as "worms," "convulsions," "thrush," and the "hooping-cough," whose epidemic nature is clearly described.

Studies on Child Development. Arnold Gesell, M.D., New York, 1948, Harper and Brothers, 224 pages. Price \$4.00.

A collection of essays and addresses which in large part have been presented from time to time by invitation before medical and scientific groups. All are concerned with child development and there is a definite continuity in the arrangement and selection. The reviewer has obtained from the book a much broader and more comprehensive picture of the work of the Yale Clinic of Child Development than he held from the separate reading of the numerous books by Dr. Gesell on individual phases of these studies. It is beyond question that Dr. Gesell's work in the field of child development is one of the outstanding contributions to pediatrics in our time. In this volume the reader obtains a picture of the breadth of his interests. The pediatrician who is chiefly familiar with such studies from the Yale Clinic as "Developmental Diagnosis" will find particular interest in some of the chapters, which are in reality summaries of some of the less familiar studies of a more psychological nature as "twin control," the essay on the conditioned reflex, and "genius and growth." The volume is good reading and will add a breadth of viewpoint to the physician working with children.

Nursing for the Poliomyelitis Patient. Prepared and published by the Joint Orthopedic Nursing Advisory Service of the National League of Nursing Education. (To all of which should be added that the preparation and publication was financed by the National Foundation for Infantile Paralysis.)

All of these organizations should be given full credit for rendering a real service by contributing to the preparation of this unusually excellent handbook of eighty-eight pages covering in detail the various phases and problems of caring for the patient with poliomyelitis. It is well written and the description of techniques and procedures are expressed in simple, clear-cut language.

While the book is primarily intended for the nurse, it is a book that every physician who has the responsibility for the care of a patient with poliomyelitis can read with profit to himself and to his patient. While the procedures described in the book are to be carried out by the nursing service, the physician is ultimately responsible for the nursing care and must have a knowledge of the nursing procedures. With the increase in the incidence of the disease this year the brochure is unusually timely.

Copies may be secured by writing the National Foundation for Infantile Paralysis, 120 Broadway, New York 5, N. Y.

Editor's Column .

A REPREHENSIBLE PETTY MEDICAL GRAFT

IN RECENT months the newspapers and lay magazines have contained numerous discussions of the "kickbacks" on eyeglasses which have finally ended in court proceedings, and whose acceptance by some ophthalmologists has brought disgrace upon the entire medical profession.

Our attention was directed a few weeks ago to another form of medical graft, petty by comparison, the sale of "professional samples." Post cards were received by St. Louis physicians from an individual in Chicago offering to buy the free samples left at our offices, and stating he would make a personal call to buy them. He also stated he had been in the "business" for a number of years.

Perhaps we live in the clouds but this was a new racket to us, although obviously it was one of some years' standing in several communities. A little investigation revealed that it is a well-organized business, and that in certain communities pickup trucks are used to carry on the work. Further, it seems there is no legal redress to stop it. In New York City, we understand, samples by law must carry the statement "Professional Sample—not to be sold," but seemingly this has little effect.

We are concerned about it as the pediatrician receives many times the samples received by practitioners in other fields, and many nonmedical items come to him in the way of foods for use in infant feeding. The selling of these professional samples is a despicable form of petty graft that is inexcusable and can only lead to the lowering of personal as well as medical standards. It offers a temptation to the young physician just starting in who has great trouble in making both ends meet, as refunds for glasses did for the young ophthalmologist. We feel that it is a serious breach of the high ethical and moral standards which the physician must hold, and individuals guilty of such practices should be expelled from our medical societies for unethical conduct in that they bring the entire profession in disrepute.

The blame cannot all be placed on the medical profession as the samples are thrust upon the physician by the commercial houses whether the doctor wants them or not. A large part comes unrequested through the mail and most of these promptly and frequently unopened find a place in the wastebasket. What becomes of these wastebasket samples in a large medical office building might well be investigated. Another large part stems from the polite and affable detail man who ends his talk by asking if he cannot send samples. It is so much easier and quicker to say "yes" rather than "no," even if the samples are not or later must be disposed of, in part at least, to make room for still more. In fact, as every pediatrician knows, the sample business can at times become an actual nuisance.

Perhaps a committee of pediatricians and the firms who furnish the samples could get together and work out some way to regulate the distribution of samples and the racket, which, if continued, cannot fail to lower the dignity and standing of the medical profession. Certainly we know of no more brazen example of contempt for the ethical standards of the physician than this open proposal to purchase "professional samples."

B. S. V.

CHILD HEALTH AND LONGEVITY

No more striking example of the effect of the child health movement in the United States can be found than in the tables of the average life expectancy in 1946, which have recently been issued by the National Office of Vital Statistics.

The average length of life at birth for a female white child born in 1946 was 70.3 years, and if she lived to be one year old, was 71.3. The white male infant had an expectancy of some five years less, the figures being 65.1 and 66.6, respectively. For nonwhite the figures are some seven and one-half years less for the male infant and nine years less for the female infant at birth.

This steady and continuing increase in the average life expectancy has been brought about chiefly by the steady decline of the infant mortality rate during the last forty years, and by control of the infectious diseases by specific preventive measures in the last twenty-five years. In the last decade the treatment of the respiratory and blood stream infections by chemical and antibiotic drugs has been a contributing factor favorably influencing the average length of life.

The average white male 65 years of age will live to be 77.6 years old, and the female of 65 to be 79.5. Thus pediatrics has led to geriatrics and a whole new set of medical, social, and economic problems.

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Original Communications

DIAGNOSIS OF PULMONARY STENOSIS BY ANGIOCARDIOGRAPHY

MERL J. CARSON, M.D., THOMAS H. BURFORD, M.D., WENDELL G. SCOTT, M.D.,
AND JAMES GOODFRIEND, M.D.†
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THE development of improved methods for the diagnosis of congenital pulmonary stenosis has become increasingly important since surgical procedures for the relief of this condition have been introduced. In addition to physical examination and roentgenographic study of the cardiac silhouette and lung fields, cardiac catheterization, oxygen consumption studies, and oximetry have proved to be valuable diagnostic aids and have achieved general acceptance. Although these studies can be carried out with relative ease on large children and adults, many technical difficulties arise when they are applied to infants. Serial contrast visualization of the cardiac chambers and great vessels (angiocardiology) has been advocated by Castellanos,¹ Sussman,^{3, 4, 5} and others⁶⁻¹² and employed by them to elucidate abnormalities present in the cardiopulmonary circulation. Although these workers have found the technique to be of great diagnostic value, it has not been widely used in spite of its many advantages. The direct information as to the course of intracardiac blood flow and relative size and location of the cardiac chambers and great vessels which can be obtained with angiocardiology has been of aid to us in establishing the exact diagnosis in several types of congenital cardiac anomalies and has been particularly helpful in differentiating the various types in which cyanosis is a prominent symptom. The method has the further advantage of being applicable to patients of all ages; diagnostic radiograms are obtained as easily in small infants as in children and adults.

PROCEDURE

In order to visualize cardiac abnormalities satisfactorily by angiocardiology, it is necessary to have equipment capable of producing a rapid sequence of radiographic exposures. Such newer automatized radiographic techniques as the tautograph* developed by one of us (W. G. S.) make this possible. The tautograph makes ten radiographic exposures within a period of ten seconds.

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†Deceased.

*A description with mechanical details is in the process of publication in the American Journal of Roentgenology and Radium Therapy.

Each patient is fasted for a period of at least four hours before the procedure. Infants and children too small to cooperate are given a general ether anesthetic. In older patients the entire operation is carried out under local Novocain anesthesia without general sedation. In patients with cyanotic heart disease and polycythemia, subcutaneous fluids are administered preoperatively to prevent dehydration, and oxygen is given concomitantly with the anesthetic.

The patient is placed on the tautograph, and with sterile technique the left or right antecubital vein is isolated by a routine cut-down procedure. The distal end is ligated, and a No. 13 or 14 cannula is inserted into the proximal end and tied in place. A slow intravenous drip of saline solution is begun through a three-way stopcock to insure patency of the cannula. The patient is placed in proper position on the table and a few minims of 70 per cent Diodrast injected through the cannula. If after several minutes no reaction has occurred, the final injection is made. Infants 3 months to 2 years of age receive 10 to 18 c.c. of Diodrast; children 2 to 10 years, 20 to 30 c.c.; and children 11 to 15 years, 30 to 40 c.c. The injection must be made as rapidly as possible in order to obtain a sufficiently dense concentration of Diodrast to insure good contrast. An injection period of longer than two seconds will seldom give sufficient contrast for diagnostic visualization of the heart or great vessels. The injection is begun immediately after the first exposure has been made.

Immediately following the injection, in the anesthetized patients, there is frequently seen a momentary irregularity of respiratory movements. In the unanesthetized patient there is often a transient feeling of increased heat, retching, and faintness. As soon as possible after the injection, the cannula is removed, the vein tied off, and the wound closed with silk sutures.

RESULTS

In order properly to interpret films showing abnormalities, it is necessary to be familiar with the normal configuration of the heart chambers and great vessels. The two most useful views are the left anterior oblique and the anteroposterior. A sequence of exposures showing the left anterior oblique view in a normal subject is shown in Figs. 1 through 6. Fig. 1 shows Diodrast immediately after injection, passing down the superior vena cava to the right auricle, into the right ventricle, and beginning to appear in the pulmonary conus where it is arching upward and backward. Fig. 2 shows better filling of the right ventricle, a fully distended pulmonary conus, and a normal-sized left and right pulmonary artery. No Diodrast is being injected in Fig. 3, and there is very good filling of the right ventricle, pulmonary conus, and pulmonary arteries. In Fig. 4 the opacification of the right side of the heart and pulmonary arteries has almost faded, but the pulmonary veins, left auricle, and left ventricle can be seen distinctly. In Fig. 5 the opacification of the right side of the heart and pulmonary arteries has disappeared. The pulmonary veins, left auricle, left ventricle, aorta, and great vessels are clearly visualized. Fig. 6 shows the same structures seen in the preceding film except that the aorta and its branches are more sharply defined, and the pulmonary veins are less distinct.

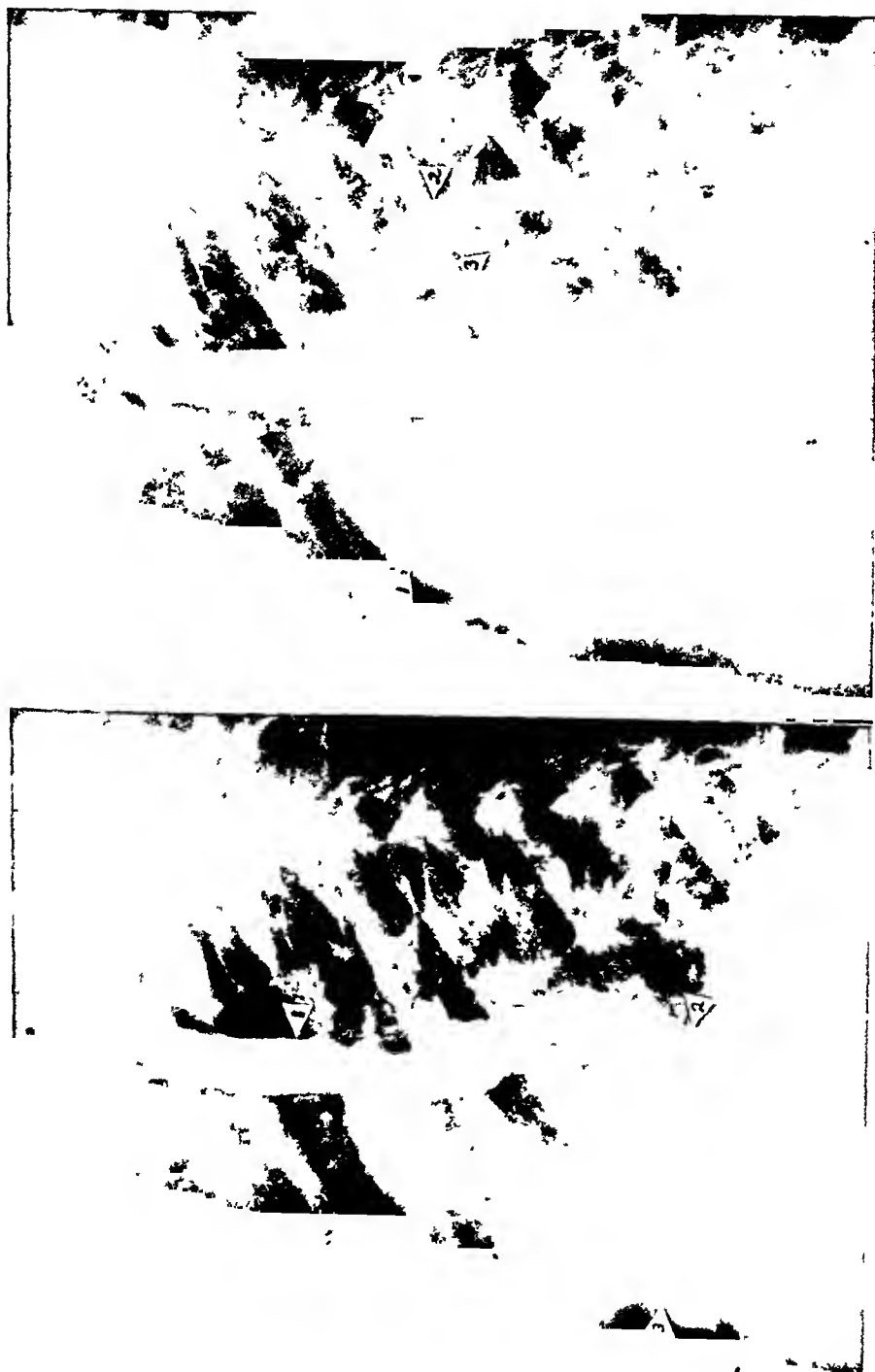


Fig. 1.

Fig. 2.

Fig. 1.—Normal angiogram, left anterior oblique. 1, Superior vena cava. 2, Right auricle. 3, Right ventricle.

Fig. 2.—Normal angiogram, left anterior oblique. 1, Pulmonary artery. 2, Left pulmonary artery. 3, Right pulmonary artery.



Fig. 3.

Fig. 3.—Normal angiocardiogram, left anterior oblique.

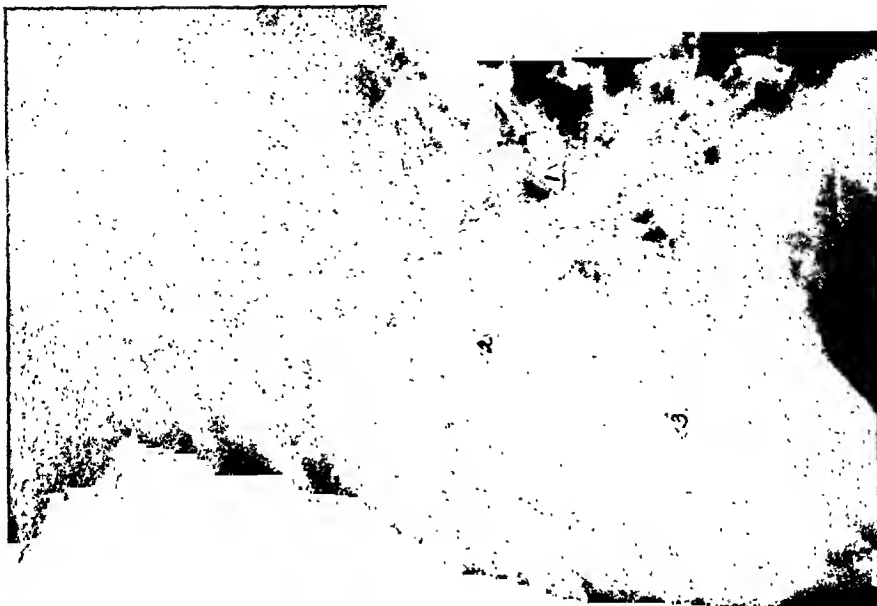


Fig. 4.

Fig. 4.—Normal angiocardiogram, left anterior oblique. 1, Pulmonary vein. 2, Left auricle. 3, Left ventricle.

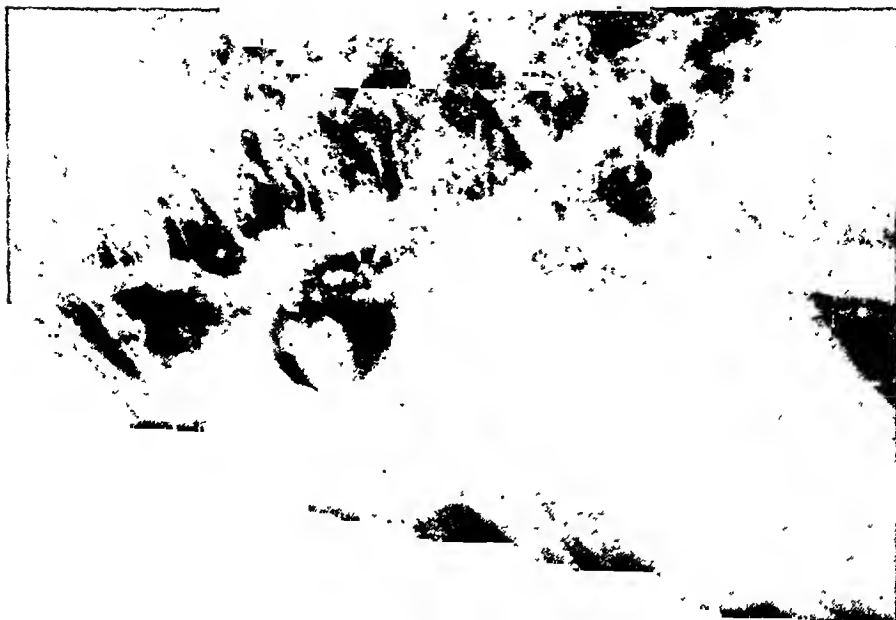


Fig. 6.



Fig. 5.

FIG. 5.—Normal angiogram, left anterior oblique. 1, Ascending aorta.
 FIG. 6.—Normal angiogram, left anterior oblique.

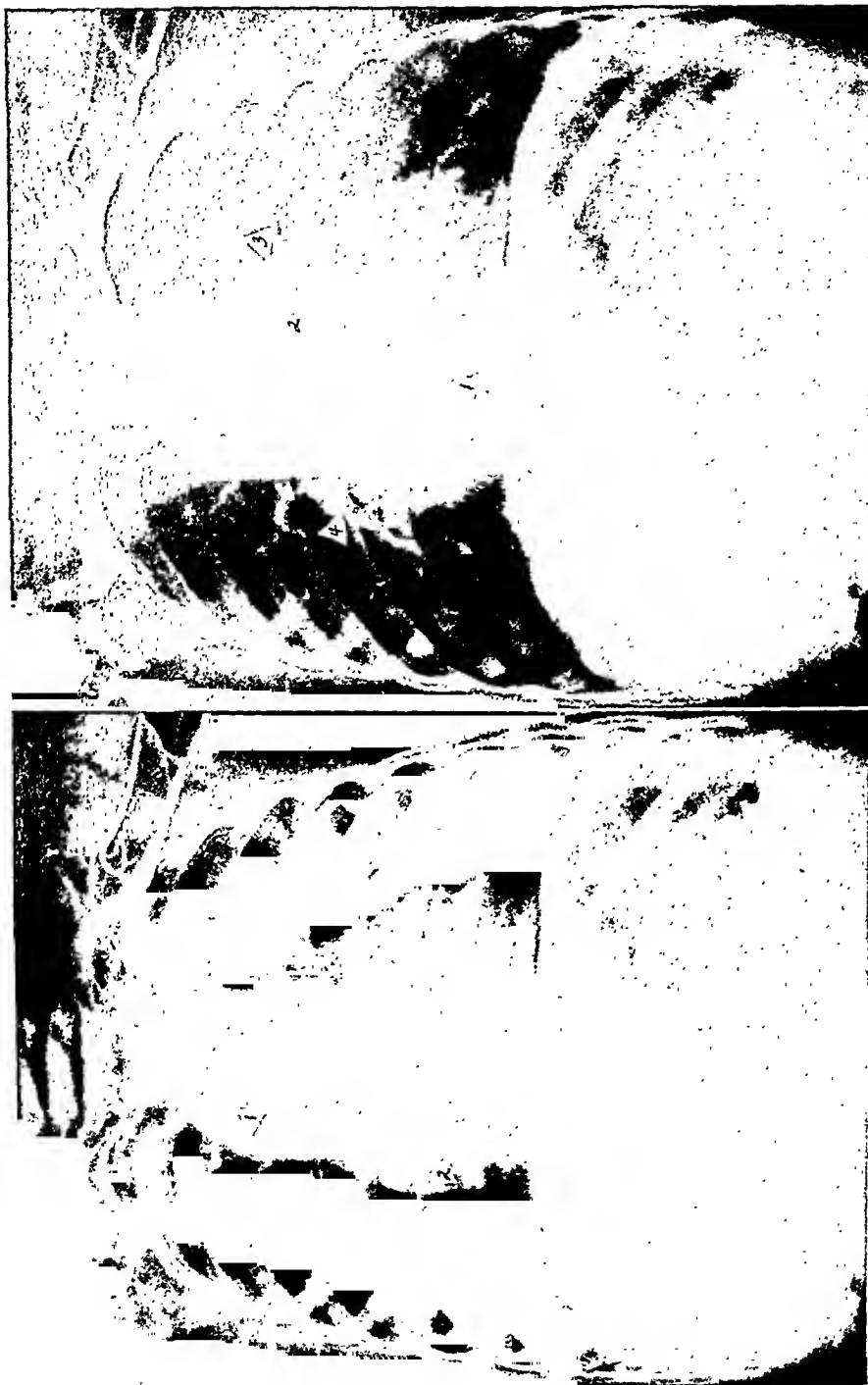


Fig. 7.

Fig. 7.—Normal angiocardiogram, anteroposterior. 1, Superior vena cava. 2, Right auricle.

Fig. 8.—Normal angiocardiogram, anteroposterior. 1, Right ventricle. 2, Pulmonary artery. 3, Left pulmonary artery. 4, Right pulmonary artery.



Fig. 9.

Fig. 9—Normal angiocardigram, anteroposterior.

Fig. 10.

Fig. 10—Normal angiocardigram, anteroposterior. 1, Left ventricle. 2, Pulmonary vein. 3, Aorta.



Fig. 11.

Fig. 11 —Normal angiocardiogram, anteroposterior.

Fig. 12.

Fig. 12 —Normal angiocardiogram, anteroposterior. 1, Left auricle.

The normal sequence in the anteroposterior view is shown in Figs. 7 through 12. Fig. 7 shows Diodrast entering through the left antecubital vein into the superior vena cava and just beginning to fill the right auricle. Fig. 8 shows complete filling of the right auricle and right ventricle. The pulmonary conus extends upward. The pulmonary artery and its bifurcation are seen at the apex of the conus, and both right and left pulmonary arteries are fully distended. As pointed out by others,¹⁶ the left pulmonary artery is seen to constitute that portion of the left cardiac border between the aortic and ventricular shadows. Fig. 9 shows a decrease in the amount of Diodrast being injected but reveals the whole right side of the heart with the pulmonary arteries in sharp relief. In Fig. 10 only a small amount of Diodrast remains in the right auricle and ventricle, and the pulmonary arteries are less well visualized than in the preceding film. The pulmonary veins, however, may be seen emptying into the centrally located left auricle, with some Diodrast being seen in the left ventricle, which is contracted in systole. The aortic arch and great vessels can also be seen. Fig. 11 fails to reveal evidence of any Diodrast in the right side of the heart or pulmonary arteries. The pulmonary veins, left auricle, left ventricle, aorta and its branches are well outlined. In Fig. 12 the same structures are visualized as in the preceding film except that the left ventricle is in systole and is not seen. The central position of the left auricle, as described previously,¹⁷ is well illustrated. It is thus shown conclusively that normally the left auricle constitutes no part of the left cardiac border.

Although it has been demonstrated that pulmonary arteries can be clearly visualized in both the anteroposterior and left anterior oblique views, the latter view is preferred since the shadows of the pulmonary arteries and aorta are separated in this position. This is essential in those types of cardiac abnormalities in which pulmonary arteries and aorta fill simultaneously.

Radiograms of four patients illustrate the value of angiocardiology in differentiating various types of cyanotic congenital heart disease.

NONFUNCTIONING RIGHT VENTRICLE WITH TRICUSPID STENOSIS

This patient, R. D., aged 14 months, was admitted with a congenital cardiac abnormality of the cyanotic type. Radiographic examination revealed a small right ventricle of the contour described by Taussig¹⁸ as characteristic of cases of nonfunctioning right ventricle; the electrocardiogram showed left axis deviation and left anterior oblique position. The anteroposterior roentgenograms obtained are shown in Figs. 13 to 15. Fig. 13 was taken just after the injection was begun and shows the superior vena cava and right auricle in their normal position. No opaque material is seen in the expected region of the right ventricle. In the center, overlying the spinal column, is the circular left auricle and just to the left of and below this structure can be seen the opacification of the left ventricle. Fig. 14 shows the same structures; in addition, reflux filling of the hepatic veins is observed. Lying to the left of the superior vena cava are the ascending aorta and aortic arch, and in the concavity of the arch is the upper portion of the pulmonary artery. Fig. 15 shows more clearly the aorta with its major branches.



Fig. 13.

Fig. 13.—Nonfunctioning right ventricle with tricuspid stenosis, anteroposterior. 1, Right auricle. 2, Left auricle. 3, Left ventricle.
 Fig. 14.—Nonfunctioning right ventricle with tricuspid stenosis, anteroposterior. 1, Hepatic veins. 2, Ascending aorta. 3, Pulmonary artery.

Fig. 14.



Fig. 15.

Fig. 15.—Nonfunctioning right ventricle with tricuspid stenosis, anteroposterior.

Fig. 16.

Fig. 16.—Nonfunctioning right ventricle with tricuspid stenosis, left anterior oblique. 1, Left ventricle. 2, Ascending aorta. 3, Pulmonary artery. 4, Hepatic veins.

The main pulmonary artery is easily seen with the right and left pulmonary arteries also visualized. Both the main pulmonary artery and its branches are smaller than normal.

Fig. 16 represents the first radiogram taken in the left anterior oblique position after the injection was partially completed. It shows complete opacification of the ventricular area. The aorta and its branches are filled, and the small pulmonary conus and pulmonary arteries can be seen. There is some reflux of opaque material into the hepatic veins.

The flow of Diodrast as demonstrated by these films is from the superior vena cava into the right auricle and then to the left auricle and into the enlarged left ventricle. Both the normal aorta and the small pulmonary conus appear to come off the left ventricle and fill simultaneously with Diodrast. The pulmonary arteries are smaller than normal. The failure of the right ventricle to visualize demonstrates either that this chamber is absent or is occluded from the circulation by an atresic tricuspid valve.

At operation pulmonary stenosis was found. Anastomosis of the left pulmonary artery to the aorta resulted in an improved pulmonary circulation with relief of the cyanosis and polycythemia.

PERSISTENT TRUNCUS ARTERIOSUS

This 16-month-old child, J. H., was admitted with congenital heart disease of the cyanotic type. Radiograms revealed marked enlargement of the heart, especially of the right ventricle. The shelflike projection of the right ventricle imparted to the organ that contour which has been described as characteristic of cases of persistent truncus arteriosus.¹⁹ The electrocardiogram gave evidence of right axis deviation. Angiocardiograms were taken in both anteroposterior and left anterior oblique positions. Figs. 17 and 18 show the latter view. In Fig. 17 Diodrast can be seen entering the superior vena cava, right auricle, and right ventricle, whence it spills over into the left ventricle. The beginning of the common arterial pathway can be visualized. Fig. 18 shows a large opaque right ventricle with an increasing amount of opacification of the left ventricle. There appears to be a defect of the interventricular septum. A single arterial outflow (truncus arteriosus) is visualized. Neither pulmonary conus nor pulmonary artery is seen.

In the anteroposterior view, Fig. 19 shows opacification of the superior vena cava, right auricle, and partially of the right ventricle. Fig. 20 shows full filling of the right ventricle with partial filling of the left ventricle apparently through a large interventricular septal defect. The single arterial pathway is beginning to be visualized. Fig. 21 shows opacification of both ventricles and the whole truncus, which is seen to lie on the right. Very small pulmonary arteries are seen, apparently arising from the common truncus.

On the basis of these studies it is felt that this patient had a persistent truncus arteriosus with very small pulmonary arteries and a large interventricular septal defect.



Fig. 17.

Fig. 17—Persistent truncus arteriosus, left anterior oblique. 2, Left ventricle.



Fig. 18.

Fig. 18—Persistent truncus arteriosus, left anterior oblique. 1, Truncus arteriosus 2, Right ventricle 3, Truncus arteriosus.



Fig 19

Fig 20

Fig 19—Persistent truncus arteriosus, anteroposterior 1, Right aortic 2, Right ventricle
 Fig 20—Persistent truncus arteriosus anteroposterior 1, Left ventricle 2, Truncus arteriosus



Fig. 21.

Fig. 21—Persistent truncus arteriosus, anteroposterior. 1, Truncus arteriosus. 2, Right pulmonary artery. Fig. 22—Tetralogy of Fallot, left anterior oblique. 1, Superior vena cava. 2, Right atrium. 3, Right ventricle.

Fig. 22.



Fig. 23.

Fig. 23—Tetralogy of Fallot, left anterior oblique. 1, Left ventricle 2, Main pulmonary artery 3, Aortic arch

Fig. 21.

Fig. 21—Tetralogy of Fallot, left anterior oblique. 1, Left ventricle 2, Main pulmonary artery 3, Aortic arch.

TETRALOGY OF FALLOT

This 12-month-old boy, P. D., was admitted with a tentative diagnosis of tetralogy of Fallot. Radiograms showed decreased pulmonary vascular markings, right ventricular enlargement, slight concavity in the region of the pulmonary conus, and a clear aortic window. Right axis deviation was seen in the electrocardiogram.

Angiocardiograms taken in the left anterior oblique position are seen in Figs. 22 to 24. In Fig. 22 there is opacification of the superior vena cava, right auricle, and right ventricle. Fig. 23 shows the same structures, and in addition beginning opacification of the left ventricle is noted. A small pulmonary conus is seen in the normal position with very small left pulmonary arteries. A small amount of Diodrast can be seen in the ascending aorta and aortic arch. Fig. 24 shows increasing opacification of the left ventricle. The small pulmonary conus and stenotic right and left pulmonary arteries are more clearly seen. The entire length of the aorta can be seen.

The early filling of the left ventricle must occur because of the presence of an interventricular septal defect. The abnormally small size of the pulmonary arteries is directly demonstrated. An overriding aorta is indicated by the simultaneous filling of the pulmonary arteries and aorta. Pulmonary stenosis was confirmed at operation.

DISCUSSION AND CONCLUSIONS

Angiocardiography has been safely utilized by numerous workers as a diagnostic aid in many cardiac conditions. It is felt this method is of great value in infants and children who are so small that cardiac catheterization is impossible or impractical. By this method one can accurately trace the course of the circulation through the heart chambers and visualize the relative size, location, and number of the great vessels.

All of the cardinal features of the tetralogy of Fallot are demonstrated in the angiocardiogram: (1) an interventricular septal defect is indicated by Diodrast flowing directly from the right ventricle into the left ventricle, producing increasing opacification of the latter in the second or third radiogram; (2) simultaneous opacification of the aorta, pulmonary conus, and pulmonary arteries indicates the presence of an overriding aorta with the Diodrast flowing simultaneously into both the aorta and pulmonary conus from the right ventricle; (3) the enlargement of the right ventricle is seen; (4) the decreased caliber of the pulmonary arteries is directly visualized. This last observation alone will serve to differentiate cases of tetralogy of Fallot from those of Eisenmenger's complex. In the latter condition pulmonary arteries of normal or unusually large size are seen (Fig. 25).

Cases of nonfunctioning right ventricle with tricuspid stenosis are characterized by the following findings: opaque material can be observed to enter the right auricle from the superior vena cava. None can be seen going into the right ventricle, but instead it can be seen entering the left auricle and then an enlarged left ventricle. Following this there is simultaneous visualization of the

aorta, and if pulmonary stenosis is present, small pulmonary arteries are visualized.

Persistent truncus arteriosus with stenotic pulmonary arteries will show the following characteristics: (1) the Diodrast reveals a very large right ventricle; (2) a large interventricular septal defect is indicated by rapid opacification of the left ventricle in the second or third radiogram; (3) in the second or third



Fig. 25.—Eisenmenger's complex, left anterior oblique. 1, Ascending aorta. 2, Main pulmonary artery. 3, Left pulmonary artery.

radiogram a single large vessel is seen emerging from the region of the ventricles, and because very rapid opacification of this vessel occurs at the same time the left ventricle begins to be visualized, it is likely that the truncus overrides the septal defect; (4) no pulmonary conus is seen, but abnormally small pulmonary arteries can be visualized arising from the single large truncus. We have not studied a case of persistent truncus in which the pulmonary blood flow is derived from the bronchial arteries.

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ECZEMA VACCINATUM: RECOVERY OF VACCINE VIRUS FROM THE CUTANEOUS LESIONS OF TWO CHILDREN AND THE DEMONSTRATION OF AN ANTIBODY RISE DURING CONVALESCENCE

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KAPOSI'S varicelliform eruption¹ is a syndrome in which individuals develop an eruption and a febrile reaction as a complication of a pre-existing eczema. In many of these individuals the secondary eruption is the result of primary infection with the virus of herpes simplex,²⁻⁵ but vaccine virus may also enter the eczematized skin and cause a clinically similar picture, eczema vaccinatum. Diagnosis of eczema vaccinatum has been confirmed by the demonstration of Guarnieri bodies in the lesions or in the tissues of inoculated rabbits⁶⁻¹² or was made because of a history of exposure to vaccinia.⁶⁻²² Few attempts have been made to identify the virus by cross-immunity studies and none to show an antibody rise in the blood of the patient during convalescence. The present report describes the recovery of vaccine virus from the acute skin lesions of two patients and the subsequent development of neutralizing antibodies against vaccinia in both patients during convalescence.

CASE 1.—C. C., a 3½-year-old Negro child, had had a generalized atopic dermatitis most marked on the face, forearms, and legs since the age of 2 years. Three days before admission to the Cincinnati General Hospital on Nov. 6, 1947, a small papular lesion was noted on the face. New lesions rapidly appeared over the face and later on the neck, arms, and legs. The mother applied penicillin ointment but the lesions progressed, the face became edematous, and fever developed. On admission the child appeared acutely ill. There was evidence of a chronic, lichenified dermatitis on the arms and legs. Over the face, arms and thighs discrete vesiculopustular, umbilicated lesions were seen (Fig. 1). The temperature was 105° F., the white blood count 16,000 with 88 per cent polymorphonuclear leucocytes. Swabs of the skin lesions taken on admission and inoculated on the scarified corneas of rabbits produced keratoconjunctivitis. In the course of the next four days the child's temperature gradually returned to normal, the lesions crusted and dried, leaving only depigmented areas and evidence of the old atopic dermatitis. No history of recent exposure to herpes or to vaccinia could be obtained. The child had not been vaccinated.

Identity of the C. C. strain.—Swabs of the patient's skin lesions taken on the day of admission were rubbed on the scarified corneas of rabbit 1. Panophthalmitis developed on the second day. The cornea and nictitating membrane of one eye were removed and after a portion of the cornea had been reserved for histologic section the tissues were pooled, ground in a mortar with saline and alundum, and centrifuged at low speed for a few minutes. A portion of the supernatant fluid was cultured on a blood agar plate and the remainder stored in the refrigerator. After twenty-four hours of incubation had revealed no

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baacterial growth, the material was rubbed with a swab on the scarified corneas of normal rabbit 2 and rabbit 3, which was immune to herpes. Panophthalmitis developed in both animals, indicating that an agent other than herpes simplex virus was present. The cornea and nictitating membrane of rabbit 2 were transferred by swab to the corneas of normal rabbit 4, and rabbit 5, which was immune to herpes, and injected intracerebrally into six mice. Again a reaction



Fig. 1—C. C. Eczema vaccinatum.

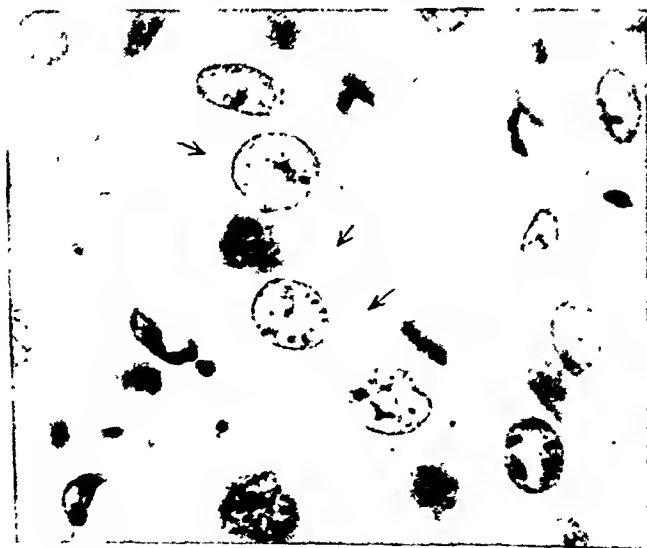


Fig. 2—C. C. Eczema vaccinatum. Intracytoplasmic inclusions in rabbit's cornea. (Hematoxylin and eosin, $\times 1000$)

occurred in the eyes of both rabbits. Sections of the corneas of rabbits 1 and 2 revealed numerous intracytoplasmic inclusions (Guarnieri bodies) characteristic of the vaccinia-variola group of viruses (Fig. 2). Intranuclear inclusions characteristic of herpes simplex were not observed. Subsequently rabbits 1, 2, and 4 were tested for immunity to the R.I. strain of vaccinia* by the combined ocular and cutaneous routes and were found to be immune. At a later date

two of these animals were challenged with the H.F. strain of herpes simplex* and were not immune. Thus it was apparent that the infectious agent recovered from the cutaneous lesions induced immunity in rabbits to vaccinia but not to herpes simplex virus. The mice injected intracerebrally remained well and a month later failed to resist cerebral challenge with herpes virus.

The results of cross-immunity tests in rabbits are summarized in Table I. Five normal control animals (1, 2, 4, 7, and 8) developed a reaction after inoculation with the C. C. strain of virus. After recovery they were immune to the R.I. strain of vaccinia. Two of these rabbits (1 and 2) were later tested for immunity to herpes virus but were not immune. Three animals (3, 5, and 6) that had previously withstood a challenge inoculation with a strain of herpes virus did not resist the C.C. strain. Rabbit 9, which had recovered from infection with the R.I. strain of vaccinia, was thereafter immune to the C.C. strain.

TABLE I. CROSS-IMMUNITY TESTS IN RABBITS

STRAIN INOCULATED	RABBIT NUMBER	PREVIOUSLY HAD RECEIVED	RESULT OF OCULAR INOCULATION			RESULTS OF IMMUNITY TESTS	
			PASSAGE INOCULATED	REACTION IN EYE	CYTO-PLASMIC INCLUSIONS	VACCINIA (R.I. STRAIN) I. CUTANEOUS	HERPES SIMPLEX (H.F. STRAIN) I. OCULAR
C.C. Case 1	1	Nothing	Original	+	+	Immune	Not immune
	2	Nothing	I	+	+	Immune	Not immune
	3	H.F. herpes	I	+	--	---	---
	4	Nothing	II	+	--	Immune	---
	5	H.F. herpes	II	+	--	---	---
	6	H.F. herpes	III	+	--	---	---
	7	Nothing	III	+	--	Immune	---
	8	Nothing	III	+	--	Immune	---
	9	R.I. vaccinia	III	0	--	---	---
R.C. Case 2	10	Nothing	Original	+	+	Immune	Not immune
	11	Nothing	I	+	+	Immune	Not immune
	12	R.I. vaccinia	I	0	--	---	---
	13	R.I. vaccinia	I	0	--	---	---

An attempt to recover an infectious agent from the patient's blood was also made. Blood obtained on the day of admission was injected by the combined intracerebral (0.03 c.c.) and intraperitoneal (0.1 c.c.) method into four young mice. A month later they were tested for immunity to the H.F. strain of herpes, and were not immune. Serum which had been kept frozen in dry-ice was thawed after nine days and rubbed on the scarified corneas of a rabbit but there was no reaction.

Neutralization Tests.—Final proof of the infection of patient C.C. by the virus of vaccinia was obtained when it was shown that serum neutralizing antibodies developed during convalescence. Sera obtained on the day of admission and again fifteen days later were tested for their neutralizing ability against the R.I. strain of vaccinia. A 10 per cent lyophilized suspension of infected rabbit testis (centrifuged suspension in undiluted rabbit serum prepared in 1944) was rehydrated and dilutions of 1:50, 1:500 . . . etc., up to

*The R.I. strain of vaccinia and the H.F. strain of herpes simplex were kindly supplied by Doctor P. K. Olitsky of the Rockefeller Institute for Medical Research, New York.

1:50,000,000 made in 10 per cent rabbit serum-saline. The virus suspensions, when added to equal amounts (0.1 c.e.) of undiluted test sera, gave final dilutions of 1:100 (10^{-2}), 1:1,000 (10^{-3}) . . . etc., up to 1:100,000,000 (10^{-8}). The mixtures of virus dilution and serum were allowed to stand at room temperature for one-half hour. A rabbit with clear skin was clipped and its skin marked off with an indelible pencil. One-tenth cubic centimeter of each serum-virus mixture was injected intraeutaneously into the marked areas and the resulting skin lesions were measured daily. Sterile skimmed milk was used as a control.

VACCINIA NEUTRALIZATION TEST

ON BACK OF A RABBIT

Skin Lesion Traced on 10th Day

Final Dilution of Virus	SERUM IN TEST		
	CONTROL (skim milk)	Patient C C , I acute	Patient C C , II convalescent
10^{-2}			
10^{-3}			
10^{-4}			
10^{-5}			
10^{-6}			
10^{-7}			
10^{-8}			

0 1 2 3 4 5
Centimeters
● = necrosis

Fig. 3.

Lesions developed within a few days but no new ones appeared after the fifth day. Whereas the acute phase serum inhibited only the 10^{-7} dilution of virus, the convalescent phase serum modified the 10^{-4} dilution and completely suppressed the formation of all lesions in a dilution of 10^{-7} or above. A tracing made on the tenth day is shown in Fig. 3.

The same sera were examined for the presence of neutralizing antibodies against herpes simplex virus. Undiluted serum was mixed with equal amounts (0.2 c.e.) of decimal dilutions of herpes virus and after an incubation period of two hours at 37° C. the mixtures were injected intracerebrally into groups

of mice. The results showed that antibodies were absent in the acute phase serum and did not appear during convalescence.

CASE 2.—R. C., a 2 year-old boy, was admitted to the Cincinnati General Hospital on March 19, 1948, because of a large purulent lesion over the right eye with swelling of the eyelids of two days' duration. He had had eczema in the past and frequent attack of scabies. On admission the patient was moderately ill and very irritable. His temperature was 103° F., the white blood count 14,800. There was edema and cellulitis of both eyelids. Over the right eye including the eyebrow and bridge of the nose was a large lesion made up of discrete and confluent umbilicated pustules with several small satellite pustules (Fig. 4). There were other small pustules on the chin, face, neck, scalp, and index finger. Over the rest of the body were many scratches, the typical lesions of scabies, some indurated areas, probably the result of chronic eczema, and much secondary infection. The child was treated with moist compresses, penicillin, benzyl benzoate, and sulfathiazole ointment. The scabies rapidly improved but the lesion above the right eye progressed, the fever continued, and the child became worse. After 5 days the temperature fell to normal, the lesion gradually crusted over and healed. A swab of the cutaneous lesions taken five days after admission was rubbed on the scarified corneas of a rabbit and keratoconjunctivitis developed. The patient had been exposed to a recently vaccinated individual.



Fig. 4.—R. C. Eczema vaccinatum.

Identity of the R.C. Strain.—A swab of the lesion on the face taken five days after admission was rubbed on the scarified corneas of rabbit 10 and keratoconjunctivitis developed in three days. The cornea of one eye was removed and elementary bodies were observed in a scraping stained by Castañeda's method and in a histologic section of a portion of the cornea. The remainder of the cornea was ground in 2 c.c. of physiological saline and centrifuged lightly

for a few minutes. Culture of the supernatant fluid on blood agar revealed no bacterial growth. The material was inoculated by the combined intrautaneous and intraocular routes in rabbits. Rabbit 11, a normal control animal, developed a skin lesion, keratoconjunctivitis, and a febrile reaction while two rabbits immune to vaccinia, 12 and 13, were resistant. After recovery from infection with the R.C. strain rabbits 10 and 11 were immune to the R.I. strain of vaccinia but not to the H.F. strain of herpes (Table I).

The corneal suspension was also injected intracerebrally into six mice. The animals remained well. At the end of twelve days one mouse was sacrificed and its brain subinoculated intracerebrally into five other mice. These animals likewise remained well. At a later date both groups of mice were found to be not immune to cerebral challenge with herpes virus.

VACCINIA NEUTRALIZATION TEST

ON BACK OF A RABBIT

Skin Lesions Traced on 7th Day

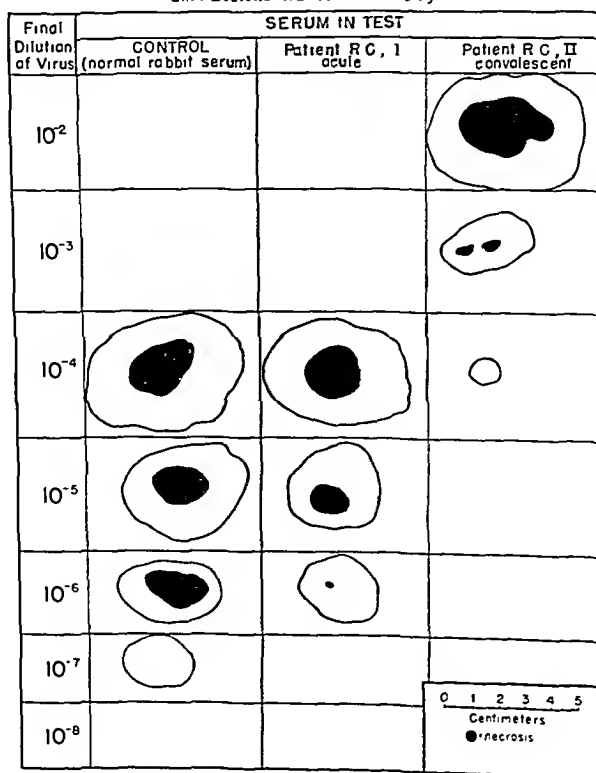


Fig. 5.

Neutralization Tests.—Acute phase serum obtained from the patient early in the course of the disease and convalescent phase serum obtained five weeks later were tested for the presence of neutralizing antibodies against vaccinia. The neutralization test was performed on the back of a rabbit, a lyophilized suspension of the R.I. strain of vaccinia being employed as before. Normal rabbit

serum was used as a control. The test (Fig. 5) showed that antibodies which were negligible in the acute phase serum developed during convalescence. Reactions to dilutions of 10^{-3} and 10^{-4} were modified and to higher dilutions completely inhibited. Antibodies against herpes virus were not found in the serum samples by the intracerebral neutralization test in mice.

DISCUSSION

Eczema vaccinatum occasionally occurs as a result of direct inoculation of an eczematous individual with vaccine virus,^{22, 23} but more commonly arises as a result of exposure to a recently vaccinated child.⁸⁻²² In a few instances vaccine virus has been recovered¹¹ or Guarnieri bodies demonstrated⁶⁻¹² in the skin lesions of the patient or in the tissues of inoculated rabbits. Apparently no attempts have been made to demonstrate a rise in neutralizing antibody titer during convalescence, although the presence of antibodies in a child after recovery has been recorded.⁸ In the present report the diagnosis of eczema vaccinatum was made in two children by the recovery from the skin lesions of an agent which was shown to be a strain of vaccine virus by histologic and immunologic means. The relationship of this agent to the infection in the children was shown by the appearance in the blood stream during convalescence of neutralizing antibodies, which were not present at the onset of the acute eruption.

SUMMARY

An infectious agent was recovered from the cutaneous lesions of two children with eczema vaccinatum. Both agents were identified as a strain of vaccinia by the demonstration of cytoplasmic inclusions in the corneas of inoculated rabbits and the development of cross-immunity in rabbits. Each patient showed a rise in neutralizing antibodies against a known strain of vaccinia during convalescence.

Grateful acknowledgment is hereby made to Mr. Joseph Homan of the Department of Medical Art for preparing the photographs.

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STREPTOMYCIN IN THE TREATMENT OF PERTUSSIS

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THIS study was undertaken to determine the effect of streptomycin* on uncomplicated pertussis.

In 1945, Bradford and Day¹ found that streptomycin is an effective agent in the treatment of experimental infection produced in mice by fresh strains of *Hemophilus pertussis*.

Hegarty and associates² tested the activity of streptomycin in vitro against strains of *H. pertussis* and found that it was both bacteriostatic and bactericidal to this organism.

A review of the literature³ at the time this study was started failed to reveal information on the effect of this agent against pertussis in humans. It was for this reason that the pilot study was undertaken. No attempt was made to compare this form of therapy with the use of human or rabbit hyperimmune serum.

PLAN OF STUDY

Only patients having uncomplicated whooping cough in either the catarrhal or early paroxysmal stage of the disease were included in this study. The patients were assigned in rotation to one of three groups. Those in the first group received streptomycin by the aerosol route; those in the second group received it intramuscularly, and those in the third received the usual symptomatic whooping cough treatment of the Cook County Contagious Disease Hospital. The latter were considered controls.

Before being assigned to a group, each patient was observed in the hospital for three days. Cough plates and blood counts were made, and the character, duration, and number of paroxysms were determined. A diagnosis of whooping cough was made only if the patient exhibited at least two of three diagnostic criteria: (1) positive cough plate; (2) a leucocytosis with a lymphocytosis; (3) typical paroxysms of coughing.

The patients were all observed in one ward. Nurses were assigned to this ward continuously. The nurses were specifically charged with the responsibility of timing each paroxysm as well as recording the number for each patient. They also noted whether or not emesis occurred and all other uncommon phenomena such as convulsions, epistaxis, cyanosis, and apnea. During the greater part of this study the nurses so assigned had no other duties. The usual nursing care was handled by other nurses in the ward. Upon completion of the three-day period of observation and upon having established a diagnosis of pertussis according to the above standards, therapy was started.

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*Streptomycin Calcium Chloride Complex, very kindly supplied by Merck and Company, Inc.

Group 1 patients received one gram of streptomycin dissolved in 8 c.c. of normal saline solution. One cubic centimeter of this solution was administered every three hours around the clock. The solution was nebulized by attaching a Vaponefrin Nebulizer* to an oxygen tank, and administered via an infant-sized B.L.B. mask. The rate of flow of oxygen was 4 to 6 L. per minute and the average period of time to administer an aerosol dose of streptomycin was from seven to ten minutes.

Group 2 patients also received one gram (one million units) of streptomycin daily, divided into eight equal doses given intramuscularly every three hours.

Black and Poneher⁵ have recently described an efficient and inexpensive mask which is being manufactured by the Vaponefrin Company. This would simplify the administration of aerosol therapy to the young infant.

RESULTS

Tables I to IV show that with the exception of one patient in the control group who died, practically all patients improved during their hospital stay. In those patients who received streptomycin, however, a more marked diminution in the average daily number of paroxysms occurred than in the control group. The average duration of paroxysms was also significantly different in the three groups.

The number and severity of complications exhibited in the control group were significantly greater than in the other groups. Two patients developed

TABLE I. AEROSOL TREATMENT

NAME	AGE	AVERAGE NO. PAROXYSMS DAILY BEFORE TREATMENT (3 DAYS)	AVERAGE NO. PAROXYSMS DAILY AFTER TREATMENT (7 DAYS)	AVERAGE DURATION BEFORE TREATMENT (SECONDS)	AVERAGE DURATION AFTER TREATMENT (SECONDS)	REMARKS
M. C.	9 mo.	25.0	8.0	20.0	27.3	Treatment stimulated paroxysms
B. B.	4 yr.	12.6	1.8	20.1	7.2	
R. E.	5 yr.	13.0	2.8	27.2	13.9	
T. J.	4 yr.	8.6	2.2	28.0	20.7	
B. S.	3 yr.	10.7	0.5	49.8	5.0	
J. P.	15 mo.	8.5	5.0	17.1	14.8	Twin
G. W.	10 mo.	23.9	9.0	56.6	50.0	
S. L.	3 yr.	10.0	4.8	26.4	28.2	

TABLE II. INTRAMUSCULAR TREATMENT

NAME	AGE	AVERAGE NO. PAROXYSMS DAILY BEFORE TREATMENT (3 DAYS)	AVERAGE NO. PAROXYSMS DAILY AFTER TREATMENT (7 DAYS)	AVERAGE DURATION BEFORE TREATMENT (SECONDS)	AVERAGE DURATION AFTER TREATMENT (SECONDS)	REMARKS
S. K.	6 mo.	18.7	7.6	35.5	40.0	Rash fourth day of treatment
L. D.	3 mo.	20.2	11.0	69.8	28.6	
L. S.	3 mo.	20.0	1.6	21.9	8.7	
J. L.	2 mo.	10.6	3.8	75.0	34.2	
S. G.	8 mo.	5.3	1.8	24.5	18.7	
N. M.	3 mo.	7.0	3.6	23.7	17.6	
P. K.	6 wk.	25.0	15.5	51.5	37.1	
R. W.	7 mo.	19.6	3.1	33.9	15.7	

*Nebulizers were very kindly supplied by the Vaponefrin Company of Chicago.

TABLE III. CONTROL

NAME	AGE	AVERAGE NO. PAROXYSMS DAILY BEFORE TREATMENT (3 DAYS)	AVERAGE NO. PAROXYSMS DAILY AFTER TREATMENT (7 DAYS)	AVERAGE DURATION BEFORE TREATMENT (SECONDS)	AVERAGE DURATION AFTER TREATMENT (SECONDS)	REMARKS
C. S.	5 yr.	6.0	8.4	12.8	21.3	Scarlet fever twelfth day
L. W.	3 yr.	19.0	9.3	53.6	36.5	Severe emesis
E. W.	6 yr.	13.6	9.5	70.7	46.2	Still vomiting on discharge
B. S.	4 yr.	24.5	11.2	54.3	67.3	Otitis media on tenth day
R. P.	15 mo.	10.0	10.0	18.9	37.3	Twin better
R. K.	2½ mo.	9.0	-	22.1	-	Died. Fifth day bronchopneu- monia
A. W.	2½ yr.	12.0	3.1	27.8	34.1	Otitis media twelfth day
S. B.	18 mo.	9.0	8.7	21.6	26.2	

TABLE IV

	AVERAGE NUMBER OF PAROXYSMS PER DAY		AVERAGE DURATION OF PAROXYSMS PER DAY		NUMBER OF CHILDREN IN STUDY
	BEFORE TREATMENT (3 DAYS)	AFTER TREATMENT (7 DAYS)	BEFORE TREATMENT (3 DAYS)	AFTER TREATMENT (7 DAYS)	
Treatment:					
Aerosol	14.0	4.3	30.6	20.9	8
Intramuscular	15.8	6.0	42.0	25.1	8
Control	13.4	8.6	37.1	38.4	7 (One died)
Differences:					
Aerosol		- 9.7		- 9.7	
Intramuscular		- 9.8		-16.9	
Control		- 4.8		+ 1.3	
Per cent change:					
Aerosol		-69.3		-31.7	
Intramuscular		-62.0		-40.2	
Control		-35.8		+ 3.5	

otitis media which was treated with sulfadiazine and one infant developed bronchopneumonia and died in spite of oxygen, sulfonamide, and penicillin treatment.

(One set of twins was observed. It was noted that the streptomycin-treated twin's disease ran a more benign course than the untreated twin, as he fed better, was not as apathetic, and had fewer and less severe paroxysms.

COMMENTS

While this is a small series of cases, it was thought by the investigators and nurses who observed each patient daily that the patients who received streptomycin via aerosol did much better clinically than the other two groups, despite the fact that the children had to be awakened to receive the treatment. This awakening frequently initiated a *paroxysm*. For this reason, the figures on the number and severity of paroxysms during the period of treatment are not recorded in this report, because they are misleading.

No toxic effects of the drug were noted with the exception of a transitory generalized morbilliform eruption which lasted two days in one patient who received streptomycin intramuscularly.

Since there had been no previous experience with streptomycin in whooping cough, our dosage of one gram a day and the length of treatment of one week was arbitrarily decided upon. From this pilot study, we believe there is sufficient evidence that streptomycin is of clinical benefit in the treatment of pertussis to justify more extended use. It also appears that the aerosol route of administration is the one of choice. This is in agreement with a statement recently made by Bradford.⁴ One week of treatment appears to be sufficient in the average case. No attempt to evaluate untoward reactions on the vestibular function to streptomycin was made, because treatment was only administered for one week.

The decrease in the number of paroxysms, the lessening of the severity of the paroxysms, the marked decrease in complications, and especially the clinical impression obtained by trained observers, all attest to the efficacy of therapy with streptomycin, especially when given by the aerosol route.

CONCLUSIONS

1. Streptomycin appears to be an effective therapeutic agent in the treatment of pertussis.
2. The aerosol route of administration is the method of choice.
3. No untoward results were noted after one week of therapy.

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VENOUS PRESSURES IN CHILDREN IN HEALTH AND DISEASE

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LOS ANGELES, CALIF.

SINCE the original determination of venous pressure by Stephen Hales¹ in 1767, little data pertinent to this measurement in children have accumulated.²⁻⁴ In 1916 Hooker,² in studying the influence of age upon venous pressure, made observations in children, using an indirect method in which the end point was determined by noting the collapse of a vein. Lambert³ found the mean venous pressure in children, using the direct method of Moritz and Tabora⁵ to be 48.4 mm. of water. Jaques⁴ using the same method determined the venous pressure on thirty-six children whose ages ranged from 7 to 15 years. His mean value was 48.3 mm. of water with a standard deviation of 15.2. Prior to 1943, most direct methods were impractical for determining venous pressure in children because of the large needles necessary for its determination.⁶ The phlebomanometer described by Bureh and Winsor⁷ proved suitable mainly because of the small needle which could be employed. The instrument is small, simple to use, and may be placed on an adjoining table near the patient. Blood loss is negligible. Multiple determinations may be made employing small veins. It is a practical portable instrument suitable for office use.

The indications for accurate direct venous pressure measurements are numerous. They are essential for: (1) the proper evaluation and treatment of many clinical syndromes such as right ventricular failure, venous obstruction, shock, edema, and disturbed water balance; (2) accurate diagnosis; (3) early and objective evaluation of therapy; (4) following the course of certain clinical states; and (5) determining prognosis. Being objective, venous pressure measurements are free from the inaccuracies of many subjective procedures.

It is the purpose of this report to: (1) establish normal values for venous pressures in children using an accurate, practical, direct venous pressure method; and (2) compare venous pressures in normal children with venous pressures in patients with rheumatic heart disease without evidence of congestive heart failure and in patients with other disease states.

METHODS AND MATERIALS

Fifty children between the ages of 3 and 10 years, with normal cardiovascular systems, were studied. In addition the following children were studied: Thirteen children with rheumatic heart disease without evidence of congestive heart failure, and four children with glomerulonephritis, one of whom showed evidence of myocardial damage but no clinical evidence of congestive failure. The subjects rested at least thirty minutes prior to venous pressure measurement, then were placed on a firm table in the supine position. The phlebotatic

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level^{8, 9} was determined, using a centimeter ruler and level. The level was placed at the fourth intercostal space and the anteroposterior diameter was measured, taking the distance from the lower portion of the level to the bed. The arm was placed at an angle of 45 degrees from the body so that the ante-cubital vein in which the venous pressure was to be measured was horizontal with one-half the anteroposterior chest diameter. This has been referred to as the phlebostatic level.^{8, 9} No talking or breath-holding was permitted. The measurement was taken using a small-gauge needle which was inserted in the direction of the blood flow.

The instrument employed recorded venous pressure in millimeters of water. A pressure-balancing bulb allowed accurate determination of the venous pressure. The size of the needle was not of great importance to the accuracy of the readings, as all readings were made when no flow of fluid in the instrument was present. A No. 25 or 26 needle was ordinarily utilized. From three to six consecutive readings were taken and the lowest pressure was recorded.

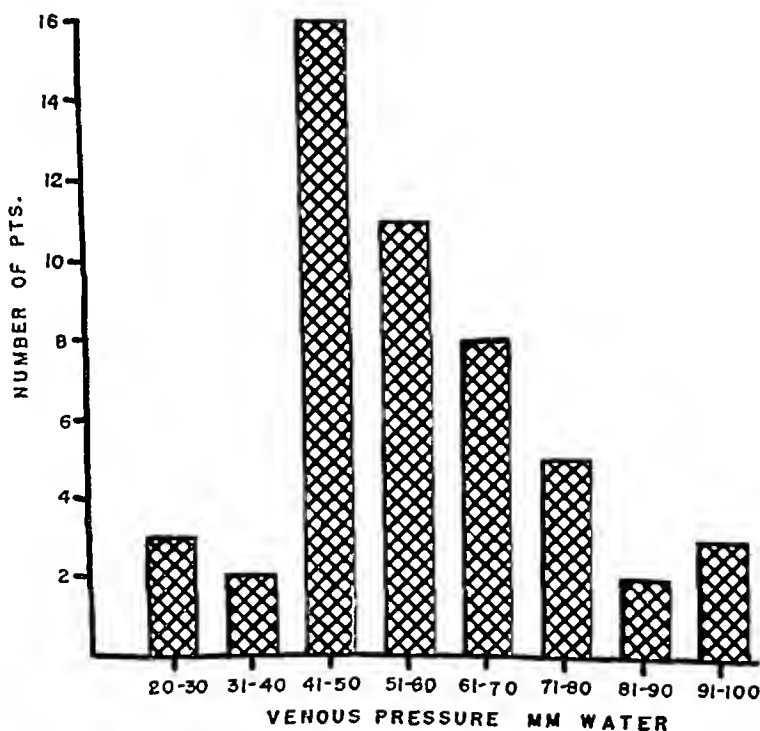


Fig. 1.—The distribution of patients at various venous pressure levels.

RESULTS

Venous Pressures in Normal Children.—The mean venous pressure for fifty children (eighteen girls and thirty-two boys), between the ages of 3 and 10 years, was 54.3 mm. of water with a standard deviation of 17.1. Eighty-six per cent of the group had venous pressures which were between 30 and 81 mm. of water. (Fig. 1.)

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Venous pressures in fifty normal subjects between 3 and 10 years of age were analyzed according to age (Fig. 2). The average in the 3-year-old group was 43.3 mm. of water; in the 6-year-old group, 60.5; in the 9-year-old group, 62.1.

Twelve subjects from 3 to 5 years of age had a mean venous pressure of 46.2 mm. of water with a standard deviation of 16.9 (Fig. 3). Thirty-eight subjects (5 to 10 years of age) had a mean pressure of 58.3 mm. of water with a standard deviation of 15.7. In general it can be seen that venous pressure increased with age.

Venous pressures were compared in male and female subjects. The average venous pressure in thirty-two males was 54.9 mm. of water and in eighteen females 53.9. These differences are not significant.

Venous Pressures in Patients With Rheumatic Heart Disease Without Evidence of Congestive Heart Failure.—The antecubital venous pressures in thirteen patients with rheumatic heart disease without clinical signs of congestive heart failure were studied (Table I). Certain patients had evidences of mild or moderate cardiac enlargement or slight abnormalities in the electrocardiogram. The blood pressures were within normal limits. None presented dyspnea, edema, râles, hepatomegaly, or clinical evidence of venous hypertension. The mean venous pressure was 92.7 mm. of water. This may be compared with the mean pressure in normal children of 54.3 mm. of water.

Venous Pressure in Patients With Acute Glomerulonephritis.—Antecubital venous pressures were studied in four patients with glomerulonephritis. Three were in the acute stage with râles and edema. Slight electrocardiographic changes were noted. The average venous pressure for this group was 97.3 mm. of water \pm 21.2 (Fig. 3).

DISCUSSION

In 1943 the phlebomanometer was utilized in determining normal venous pressures in adult individuals. The average pressure was 97 mm. of water. This is considerably higher than for individuals between the ages of 3 and 10 years, whose average venous pressure was 54.3 mm. This is in keeping with Hooker's findings of a gradual increase in venous pressure with age.² To our knowledge, normal values for venous pressure in individuals below 3 years of age are not known.

In children, as in the adult, there were no significant differences between venous pressures in male and female.

In adult individuals, when the phlebostatic level is used, chest thickness does not materially influence the venous pressure. For example, in adults whose phlebostatic levels averaged 126 mm., the venous pressure was 103 mm. of water; in those whose phlebostatic levels averaged 89 mm., the venous pressure was 104 mm. of water.⁸ In children, however, using the same method, the venous pressure increases as the thickness of the chest increases. This may be due to the increase in the venous pressure with age. Children whose phlebostatic levels averaged 60 mm. had venous pressures averaging 40 mm. of water. Those with phlebostatic levels averaging 75 mm., had venous pressures averaging 64 mm. of water.

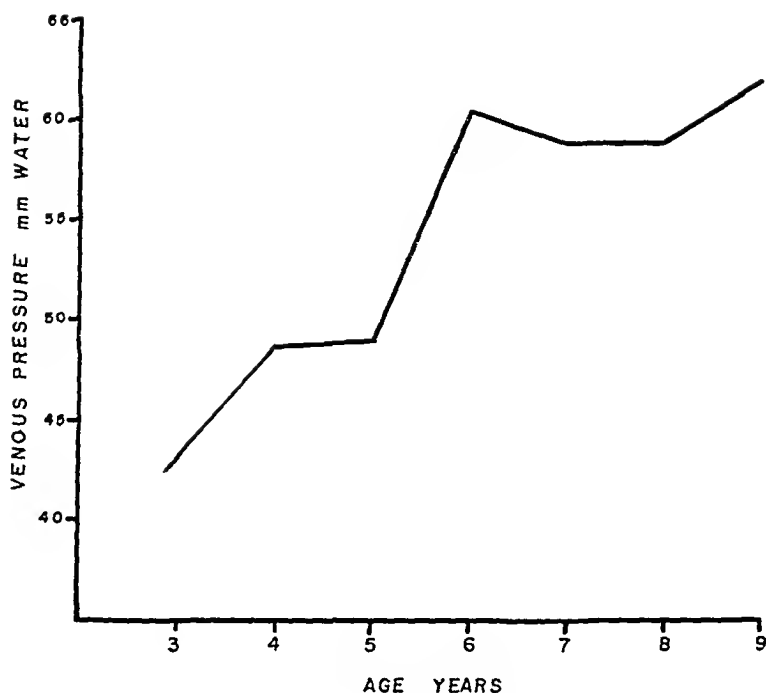


Fig. 2.—The relation of venous pressure to age, using the phlebomanometer and the phlebo-static level as a point of reference.

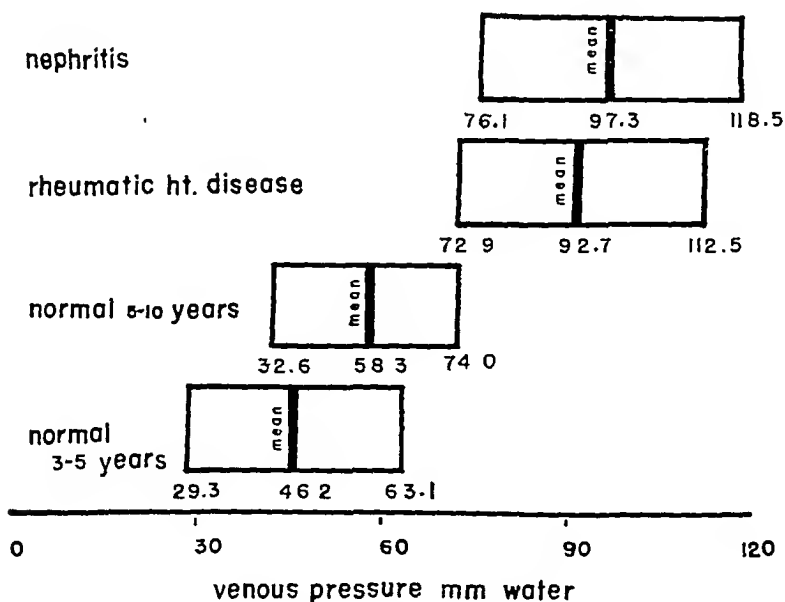


Fig. 3.—Mean venous pressure levels and standard deviations of normal children from 3 to 5 years and from 5 to 10 years of age as compared with the thirteen patients with rheumatic heart disease without clinical evidence of heart failure and the four patients with glomerulonephritis.

The direct method was ordinarily a suitable procedure for determining venous pressure in patients 3 years of age or older. In younger patients there was difficulty in securing cooperation. Most accurate venous pressure measurements were determined when the veins were punctured on the first attempt. It was usually accomplished using a No. 25 or 26 needle. Undue trauma caused venospasm and poor cooperation with elevation of the pressure. It should be pointed out that the position of the arm is important. Ideally, the arm was held at approximately 45 degrees from the body. When close to the body, there was often venous obstruction. This likewise occurred when the arm was greater than 90 degrees from the body.

In the above experiments the needle was inserted in the direction of the blood flow. It has been shown that differences in placement of the needle in regard to the direction of the flow produces some differences in pressure. The average difference in the adult was approximately 15 mm. of water. This difference was particularly noticed when small veins were used. Thus in the determination of venous pressure in children, it is essential that the needle be placed in the direction of the blood flow if comparable readings are to be expected.

Venous pressures differ in various veins of the body. Venous pressure is ordinarily higher in veins more distal to the heart. In normal adults, comparative venous pressures are approximately as follows: Antecubital, 97 mm. of water; femoral, dorsal, metacarpal, malleolar, and pedal pressures are 111, 120, 150, and 176 mm. of water, respectively. Thus determinations made in veins other than the antecubital veins require different interpretation. In adults venous pressures in the right and left antecubital veins are essentially the same. It is probable that this also holds true for children. It has been said that the pressure in the veins of the left leg is somewhat higher than that of the right leg. This is allegedly due to the crossing over of the sigmoid and other structures and compression upon the left iliac vein. This, however, has not been confirmed by all observers.

There is a daily variation of venous pressure in the adult, with higher evening readings. This variation may represent a change of as much as 39 mm. of water throughout a twelve-hour period. It is probable that the venous pressures in children undergo the same daily variation. The present venous pressure determinations were made at varying periods during the day, no attempt being made to control this factor. As about half of the venous pressure determinations were made in the evening, the extreme upper limits would include the higher pressures reached. Thus the range of normal is necessarily wide.

Consecutive daily pressures in adults recorded under similar conditions at the same time of the day showed a variation as much as that shown during the course of a single day. It is likely that a similar variation occurs in children. Such daily variations, however, do not invariably occur. In one child in whom venous pressures were determined daily for four days, at different times of the day, the venous pressures were 75, 75, 80, and 58 mm., respectively.

The establishment of normal venous pressure levels in children is essential to the proper classification of many disease states. Venous hypertension, venous normotension, or venous hypotension may exist. In the age group 3 to 10 years,

TABLE I. VENOUS PRESSURES IN THIRTEEN PATIENTS WITH RHEUMATIC HEART DISEASE WHO EXHIBITED NO CLINICAL MANIFESTATIONS OF CONGESTIVE HEART FAILURE

NO	PA- TIENT	AGE (YEAR MONTH)	DIAGNOSIS	A P DIAM ETTER OF CHIST (CM.)	VENOUS PRES SURI	CARDIO- THIO- RATIO (%)	DIOI TALIS	R LITS	EDEMA	DYSP- NIA	BLOOD PRLS SURI	1 CC FINDINGS
1.	D J.	5 3	Acute myocarditis	13	55	54	0	0	0	0	95/50	Left axis deviation
2.	P R.	6 0	Acute myocarditis	16	93	52	0	0	0	0	110/90	Normal axis deviation
3.	B M.	6 5	Acute myocarditis	16 1/2	91	50	0	0	0	0	110/70	Normal axis deviation
4.	J. L.	6 6	Chronic myocarditis	13 1/2	75	57	0	0	0	0	94/40	Normal axis deviation
5.	Z A.	6 7	Mitral insufficiency	14 1/2	71	53	0	0	0	0	85/0	Slight left axis deviation
6.	L D.	6 8	Acute myocarditis	14	55	50	0	0	0	0	110/70	Normal axis deviation. P R. interval 0.17 sec.
7.	N R.	7 0	Chronic myocarditis	17	75	48	0	0	0	0	100/60	Slight right axis deviation
8.	M S.	7 6	Mitral insufficiency	16	116	46	0	0	0	0	105/70	Normal axis deviation
9.	D W.	9 0	Mitral insufficiency	14 1/2	89	51	0	0	0	0	?	Normal axis deviation. P R. interval 0.16 sec. Wandering pacemaker
10.	R. M.	9 6	Mitral valvulitis	15	107	54	0	0	0	0	125/85	Slight right axis deviation
11.	R C.	9 9	Mitral insufficiency	15 1/2	108	-	0	0	0	0	115/65	Right axis deviation
12.	L B.	10 0	Mitral stenosis and insufficiency	15	77	66	0	0	0	0	105/55	Right axis deviation
13.	R. C.	10 8	Mitral stenosis and insufficiency	17	107	42	0	0	0	0	110/70	Normal axis deviation

In the treatment of patients with cardiac disease in whom intravenous therapy, particularly plasma and blood, is administered, venous pressure determinations are highly desirable in controlling the amount and rate of speed of administration. It was noted in one patient with nephrosis, whose resting venous pressure was 54 mm. of water, that the intravenous administration of serum albumin increased the pressure to 69, 97, and 117 mm. of water following the administration of 20, 50, and 75 c.c. of 25 per cent serum albumin, respectively. Thus the administration of 75 c.c. of 25 per cent serum albumin produced an increase of venous pressure which was 100 per cent above the child's normal value.

SUMMARY

The antecubital venous pressure was studied in fifty normal children and in groups of patients with rheumatic heart disease without clinical evidence of congestive heart failure and in patients with glomerulonephritis. The mean venous pressure for normal children between 3 and 10 years of age was 54.3 mm. of water with a standard deviation of 17.1. Between the ages of 3 and 5 years, the mean pressure was 46.2 mm. of water, ± 16.9 . Between the ages of 5 and 10 years the mean pressure was 58.3 mm. of water, ± 15.7 . The venous pressure increased with age. Patients with rheumatic heart disease without evidence of congestive heart failure and patients with glomerulonephritis had higher venous pressures than did normal individuals. The determination of the presence of venous hypertension, venous normotension, or venous hypotension is of importance, and can be readily ascertained.

We are grateful to Mr. Jack Haverback for the statistical evaluation of this study.

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venous hypertension probably would exist when the antecubital venous pressure is greater than the maximum attained in this series, i.e., 100 mm. of water; and it would possibly exist when the pressure is above 71.4 mm. of water. Venous hypotension would probably exist when the venous pressure is below 24 mm. of water; and it would possibly exist when it is below 37.2 mm. of water. Venous normotension would possibly range between 37.2 and 71.4 mm. of water and probably range between 24 and 100 mm. of water.

Venous hypertension may be either generalized or localized. A generalized increase as detected by multiple venous pressure determinations is caused by right ventricular congestive heart failure; valvular heart disease, especially tricuspid stenosis; congenital cardiac anomalies—for example, congenital tricuspid stenosis; pericarditis, either constrictive or effusive; or following or during intravenous medication, particularly plasma, blood, or serum proteins.

Localized venous hypertension may result from obstructions arising within the vein, i.e., thrombosis or embolism; changes in the vessel wall, i.e., torsion or phlebitis; and changes external to the vessel wall when obstruction is produced, i.e., neoplasia or adhesions.

Venous hypotension is found in patients with shock or peripheral circulatory collapse.

It is possible that the venous pressure is elevated in patients with rheumatic heart disease before other clinical signs of failure are evident. In these patients, many of whom had rheumatic mitral stenosis and/or insufficiency and right axis deviation in the electrocardiogram, there was an increase in the venous pressure. There was, however, no other evidence of congestive heart failure. Large hearts, as measured by the cardiothoracic ratio and as determined fluoroscopically, were sometimes present. It has been said that a large heart is a failing heart. If this is the case, it is probable that an elevated venous pressure is an earlier indication of failure than is edema. It is possible that an elevated venous pressure is the earliest sign of right ventricular congestive heart failure. On occasion, the venous pressure was high when cardiac enlargement was not demonstrable. This may be due to difficulty in demonstrating right ventricular enlargement by x-ray. For example, R.C. (Patient 13) in Table I showed a cardiothoracic ratio of 42 per cent and a venous pressure of 107 mm. of water. The heart in this instance was not clinically enlarged, and the electrocardiogram was within normal limits; however, mitral stenosis and insufficiency were present.

The venous pressure was elevated in four patients with glomerulonephritis. One of these patients showed clinical signs of myocardial damage, but none exhibited clinical evidence of cardiac failure. A high incidence of cardiac involvement is known to occur in this disease.

In congenital heart disease, right axis deviation and right ventricular strain associated with a right auricular strain is a common finding. Not uncommonly an elevated venous pressure is one of the earliest signs of failure of the right side of the heart.

In patients with pericarditis, the venous pressure is often of considerable aid in diagnosis as well as in therapy. A rising venous pressure, particularly when associated with a falling arterial pressure, is ordinarily an indication for surgical intervention.

EXPERIMENTAL RESULTS

In all the illustrations, the upper tracing of each figure is the left hand, and the lower tracing is the right hand.

Figs. 2, *a* and 2, *b* are examples of tracings of two controls. The first is that of a normal adult; the second that of a patient with rheumatic fever but no chorea. These results were obtained on the first trial. The controls were able to bring the needle up to the base line and keep it on the base line with small variations during the ninety-second revolution of the kymograph drum. The record of a mentally deficient patient is shown in Fig. 2, *c*. His attention

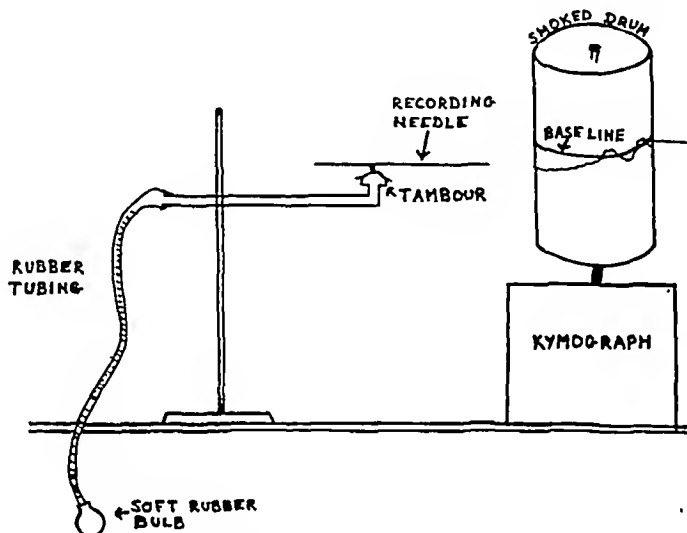


Fig. 1.—Diagram of the apparatus.

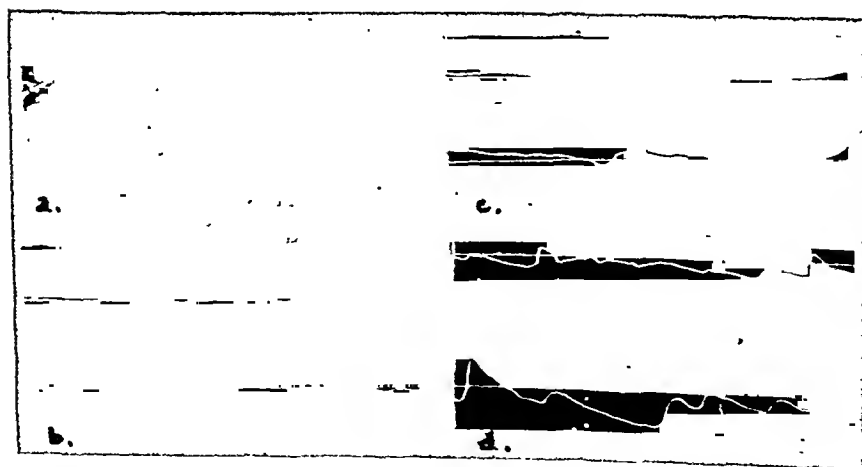


Fig. 2.—The upper tracing in each figure is the left hand, and lower tracing is the right hand. *a.* Normal adult. *b.* Nine-year-old patient with rheumatic fever, but no chorea. *c.* Nine-year-old mental defective patient, unable to cooperate in the test. *d.* Nine-year-old patient with rheumatic fever and active chorea.

THE SQUEEZOGRAM: AN OBJECTIVE METHOD FOR RECORDING THE COURSE OF CHOREA

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DURING the past years, many types of therapy have been used for chorea. Some have enjoyed only brief favor;⁴ others, such as fever therapy,¹ the ketogenic diet,² and phenyl-ethyl-hydantoin (Nirvanol),³ are currently in use. The evaluation of these various measures has been hampered by the lack of an objective method for recording the severity of the disease and its course during therapy. Although electroencephalography,⁵ electromyography,⁶ and other technical procedures⁷⁻⁹ will reveal definite abnormalities in the choreic patient, these methods offer obvious difficulties for routine use. The need for a bedside method of recording the severity of the movements led us to adopt the simple mechanical device described below, which, for want of a better term, we have called the "squeezogram."

PROCEDURES

The apparatus used to record graphically the severity of choreiform and other types of movements is shown diagrammatically in Fig. 1. A small, soft rubber bulb of the aseptic syringe type is connected to the tambour by rubber tubing. Changes in pressure on the bulb are transmitted to the tambour. These vibrations are recorded on a smoked drum.

In conducting the test, a horizontal line is drawn on the drum. The needle is adjusted so that it rests about one centimeter below the base line. The patient is instructed to squeeze the bulb so as to bring the needle up to the base line and to maintain it at that level. All distracting factors are removed from the subject's attention, and all recordings are done in a quiet room with only the observer and the patient present. It is emphasized to the patient that he is not competing, merely that a routine record is being made. Remarks are never made regarding poor tracings; and when the subject himself notices increased movements, he is reassured as to their implication.

The subjects of these experiments were patients with chorea on the wards of Bellevue Hospital between July, 1947, and January, 1948. As controls, a number of patients admitted to the Children's Medical Service with diagnoses other than chorea, and a few normal adults were studied with the procedure outlined above.

Under the same general conditions, recordings of other diseases with involuntary movements were obtained. Patients with delirium tremens on the alcoholic wards, and patients with Parkinson's disease in the neurology department were the subjects of these observations.

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on the test could not be maintained and he showed irregularities on several attempts. In Fig. 2, *d* a tracing is shown of a choreic patient. The typical irregular movements are well demonstrated here.

Fig. 3 consists of three groups of serial recordings of choreic patients. Some of the patients showing abnormal tracings had two or three tracings taken in a single day. They were compared to determine the influence of practice. No changes were found on recordings taken during a single day.

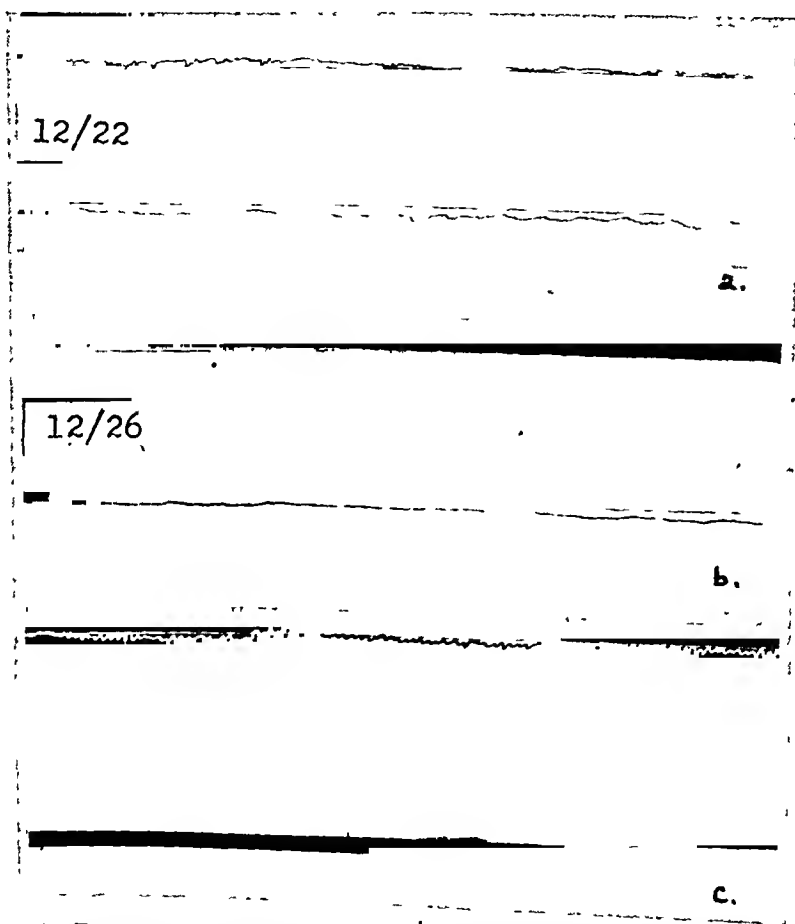


Fig. 4.—Tracings are reproduced in their actual size. In each figure the upper tracing is the left hand, and the lower tracing is the right. *a.* Patient with delirium tremens on admission. *b.* Same patient four days later. *c.* Tracing of patient with Parkinson's disease.

In Fig. 3, *a* are samples of serial recordings of a 5-year-old boy (R. B.) admitted with severe chorea. As is seen in the initial tracing, the left hand was quite normal. The right hand had marked choreiform movements which in subsequent tracings progressed gradually to normal.

Fig. 3, *b* represents recordings from a 9-year-old girl (F. S.) with moderately severe chorea who had been hospitalized for many weeks before observations were begun. The first three tracings reveal a gradual improvement. On

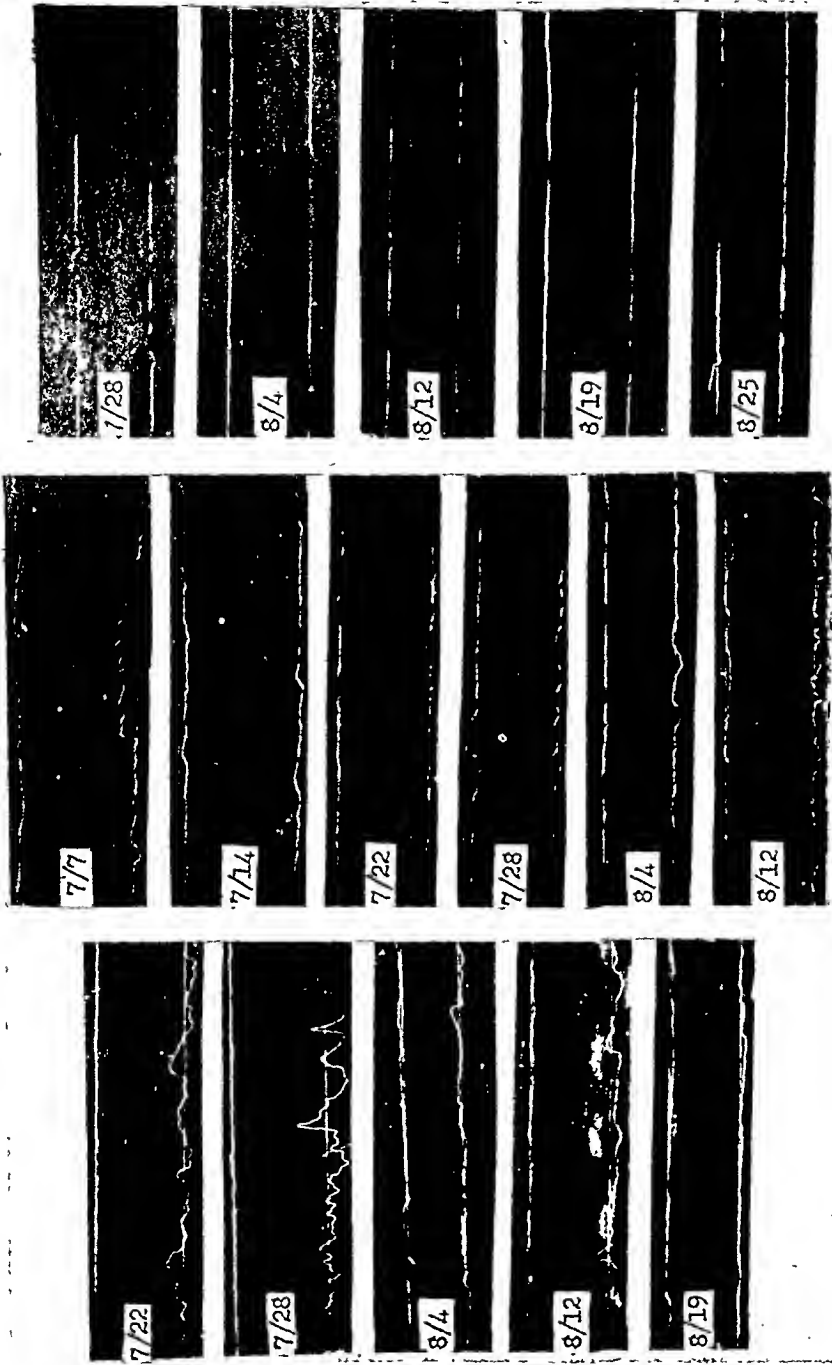


FIG. 3.—Serial records of patients with chorea. In all figures, the upper tracing is the left hand; the lower tracing is the right hand. *a*, Patient R. B., with hemichorea, demonstrating gradual improvement. *b*, Patient F. S., recording long-standing mild chorea with one relapse (July '28). *c*, Patient M. S., with normal hand tracings although she had choreiform movements of the face.

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July 28, a temporary relapse is recorded. It was independently agreed that she had become more severe clinically at that time. The patient then went on to a long course of mild chorea.

Fig. 3, *c* shows the tracings of an 11-year-old girl (M. S.) admitted with a two-week history of grimacing, involuntary hand movements, twitching, and loss of coordination. The first recording was taken after she had completed a forty-eight-hour period of starvation and when she had just been started on a ketogenic diet. This shows only an isolated incoordinated movement; but twitching was still seen about the mouth. All the following recordings were quite close to what may be considered normal. In spite of cessation of hand movements, she still manifested choreic movements of her facial muscles and tongue. These latter movements diminished in activity through the first four recording. By the fifth tracing, all clinical signs had disappeared. In this case, the tracings do not represent the true course of her chorea. Such cases must be followed by clinical observation, as no objective technique can be applied easily.

The tracings in Fig. 4 (4, *a* and 4, *b*) are those of a 54-year-old man (B. H.) admitted to the alcoholic ward with delirium tremens. He demonstrated a fine hand tremor superimposed on a coarse tremor of his whole arm. The first record shows this fine hand tremor superimposed on the wavering line. A recording taken four days later (4, *b*), when no fine tremor or coarse tremor of his arm could be demonstrated clinically, showed only a suggestion of tremor.

The tracing of a patient (P. W.) with the tremor of Parkinson's disease is shown in Fig. 4, *c*. Clinically the tremor was very overt in his left hand, while none was noticeable in his right hand. This is borne out by the tracing.

DISCUSSION

The experience which we have had with the squeezogram has shown that it will record objectively the course of chorea. It may, therefore, be applied to evaluating therapeutic procedures. The apparatus is simple and readily available. Frequent records may be easily taken and the results permanently appended to the patient's charts. However, it must be pointed out that this technique is limited by recording only abnormal movements of the hand. This is amply demonstrated by the tracings of Patient M. S. in Fig. 3, *c*. Although she had choreiform movements of the face, her squeezograms were perfectly normal.

It is interesting to note the differences in tracings from other involuntary movements. Those of chorea are coarse, irregular, and uncoordinated. The movements in delirium tremens and Parkinson's disease are fine and regular, and show coordination. The tracings illustrate well what has been noted clinically.

SUMMARY

A simple graphic method for recording the severity of choreiform movements is described. This permits a more exact evaluation of therapeutic agents than has heretofore been possible.

calories per kilogram after the third or fourth week, showed, as might be expected, a less rapid early weight gain and a more rapid one than ours in the later weeks of observation. Although the expected weight gain is, therefore, affected by the calorie intake, the feeding policies employed in this country vary within relatively narrow limits and hence we believe that the weight chart shown will prove useful even under slightly different conditions than those in our clinic.

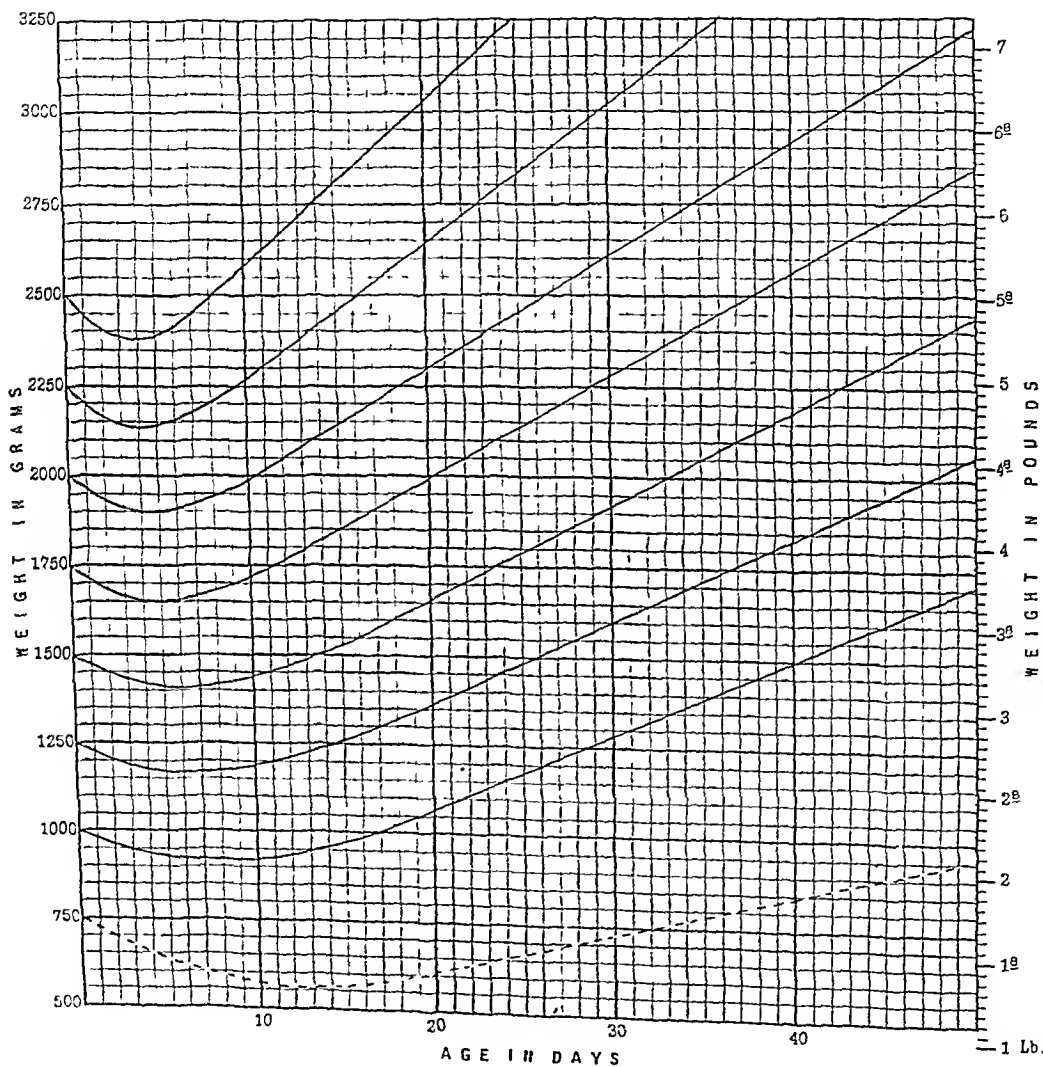


Fig. 1.

In the smallest weight group, below 1,000 Gm. birth weight, we have not found it possible to routinize our feedings and it is often necessary to proceed at a slower rate of increase than that given above. The dotted line shown for

A GRID FOR RECORDING THE WEIGHT OF PREMATURE INFANTS*

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ALTHOUGH the weight curve of the normal full-term infant is probably as well known as any pediatric datum, there is surprisingly little information as to the gain in weight of premature infants of various birth weights. The only statistical compilation with which we are familiar is that of Dunham, Jenss, and Christie,¹ who reported a composite weight curve of a group of premature infants between 1,900 and 2,000 Gm. at birth who were followed for twenty days only. It seemed to us highly desirable to have a grid showing the weight expectancy curves of premature infants of various sizes as a standard of reference for their progress, and we accordingly undertook to construct one from data of infants cared for on the Bellevue Hospital premature unit.

The weight curves of 100 premature infants ranging from 1,000 to 2,500 Gm. at birth who had exhibited no untoward complications in the neonatal period were superimposed and "normal" curves were drawn by inspection to conform to the growth patterns so revealed. The accompanying chart (Fig. 1) illustrates the result obtained.

No attempt was made to achieve statistical accuracy in constructing these curves. They do not represent average performance of children on our unit. They represent what the premature infant who develops without complications will do when fed and handled in a certain arbitrary manner, and as such we have found them exceedingly helpful in measuring the progress of our current cases. They are also useful in making comparisons of different foods.

The chief variable in determining the weight curve of such a premature infant is the feeding policy. The routine for the children used in constructing the chart consisted of a regular stepwise increase in the food beginning on the second day of life up to a total of 120 calories per kilogram which was attained on the tenth day of life and was not further increased. Olate was used as the feeding in all instances. We have been interested in comparing these curves with data from two other institutions where a somewhat different feeding routine was followed. The report of Gordon, Levine, and McNamara,² from the New York Hospital in which an adequate calorie intake was achieved by the seventh rather than the eleventh day, indicates that a somewhat more rapid increase of weight can be obtained during the first three weeks than we have shown. Conversely, data from a group of premature infants from the Boston Lying-in Hospital analyzed by Clifford and Winter,³ in which a more conservative early feeding policy was pursued followed by an increase in calorie intake above 120

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*Exhibited at the Fifth International Pediatrics Congress, New York City.

EXPERIENCES WITH EPIDEMIC DIARRHEA OF THE NEWBORN

THE USE OF NUTRAMIGEN IN ITS DIETARY MANAGEMENT

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INTRODUCTION

BETWEEN July 26, 1944, and Oct. 10, 1946, a large number of cases of epidemic diarrhea of the newborn appeared in the Philadelphia area. Many of these infants were transferred to the Children's Hospital of Philadelphia for treatment. Here, in spite of careful isolation measures, the infection spread to patients admitted for other disorders. Although not all newly born, many of these secondarily infected infants presented similar clinical courses and showed no parenteral infections. A series of seventy-five patients is studied in this paper, of which sixty-three were admitted from nurseries definitely known to be infected with this disease; the remaining twelve acquired their infections in the Children's Hospital. Only those patients who showed no parenteral infection on admission were included in this series unless it was clearly established that such infection was a complication of a pre-existing diarrhea.

PLAN OF TREATMENT

At the time of admission, most of the infants were believed to be acidotic and the carbon-dioxide combining power was determined in forty-eight cases. Often it was necessary to administer fluid before the sample of blood was withdrawn because of the shocked condition of the patient. Hydration was accomplished first by the intravenous administration of 5 per cent glucose in physiologic saline, followed by the administration of $\frac{1}{6}$ molar sodium lactate, the amount of which was adjusted according to the formula of Hartmann and Senn.¹ Half of the sodium lactate was given intravenously and half subcutaneously. In most of the cases this was followed by the intravenous administration of plasma, or, if the infant was anemic, whole blood. In a few cases 5 per cent solution of casein hydrolysate² was given intravenously. During the period of hydration, oral fluids were withheld or greatly restricted, according to the severity of the diarrhea, for periods ranging between 12 and 72 hours, until tolerance to oral feeding was regained. Oral feeding was recommenced in the form of 5 per cent glucose in physiologic saline in small, frequent feedings. If these were well tolerated, the next oral feeding offered was a rice gruel of 5 per cent strength, prepared by long cooking in a double boiler. In some cases other feedings were used in place of the rice gruel; among these were emulsions of dried apple or banana, weak tea, barley water, or farina gruel.

¹From the Department of Pediatrics, School of Medicine, University of Pennsylvania, and the Medical Services of the Children's Hospital or Philadelphia.

²Amigen solution, Mead Johnson and Company.

infants weighing 750 Gm. at birth represents observations on a very few infants of this weight who have survived.

SUMMARY

A grid is presented showing expected weight curves for premature infants of varying birth weights. Its usefulness and limitations are discussed.

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in their first. In their first epidemic, in the nursery of a general hospital, only 3.5 per cent died; in their second epidemic in the same institution 23.8 per cent died. The first thirty-seven cases of our series had a mortality rate of 37.8 per cent, while the second thirty-eight cases had a mortality rate of 10.5 per cent.

2. *Interval between onset and admission:* This period was brief in many cases where death occurred and long in many patients who survived. It could not be correlated with the prognosis in this series.

3. *Resumption of milk:* Many infants were found to have recurrences when milk was added to the glucose or rice gruel. In those whose milk was added in the form of Nutramigen, this seemed to occur less frequently. The recovery rate of the patients fed Nutramigen seems better than those fed on other forms of milk. The number of cases is small, and other factors, such as lower virulence, may be partly responsible for the better results.

4. *Relapses:* These occurred in thirty-six of our seventy-five patients, or 48 per cent. They have been referred to as the "biphasic course" in other papers. Of the thirty-six infants who had relapses, ten died, or 27.7 per cent, little above the mortality rate of the group as a whole (24 per cent).

5. *Severity of the acidosis:* In forty-eight infants the plasma carbon-dioxide combining power was determined before fluid was administered. The results in these infants were as follows:

ADMISSION PLASMA CO ₂	RECOVERED	DIED
Less than 9 meq./L. (20 volumes per cent)	10	3
Between 9 meq./L. and 13 meq./L. (20 to 30 volumes per cent)	7	6
Over 13 meq./L. (30 volumes per cent)	18	4

From these data it is impossible to make any correlation between the severity of the acidosis and the prognosis.

6. *Birth weight:* In an attempt to determine whether or not the larger infants had a better chance of recovery, the following data were collected:

BIRTH WEIGHT	RECOVERED		DIED	
	NUMBER	PER CENT	NUMBER	PER CENT
Under 2,500 Gm. (5 lb. 8 oz.)	3	27.3	8	72.7
Between 2,500-3,200 Gm. (5 lb. 8 oz.-7 lb.)	30	82.3	6	16.7
Over 3,200 Gm. (7 lb.)	19	90.5	2	9.5

A definitely lower mortality is seen in the infants of greater birth weight and a very poor prognosis can be assumed from the data of the infants weighing less than 2,500 Gm. (5 pounds 8 ounces) at birth.

7. *Extent of the weight loss before admission:* The difference between the birth weight and the admission weight was ascertained in sixty-four cases. In some infants there had been substantial gains of weight before the diarrhea began: in spite of great losses of weight, some of these infants were still above birth weight. In most cases the maximum weights were not available; as most of them were newborn the maximum weight must have been near the birth weight. The following results were obtained in sixty cases:

Milk was resumed in some of the patients by using a number of milk products such as casein powder, boiled skimmed milk, skimmed lactic acid milk, and powdered protein milk. In the course of empiric trial, we found that the resumption of milk feeding in the form of Nutramigen* was effective and perhaps better than other types of milk addition.

AN ILLUSTRATIVE CASE

The case of R. D. (45-3457) illustrates the method of treatment with Nutramigen. This infant developed diarrhea in a contaminated nursery, was removed to the Children's Hospital in advanced dehydration and with seelerema. Its weight had fallen from 3,200 Gm. (7 pounds, 2 ounces) to 2,550 Gm. (5 pounds, 10 ounces). Where elyses had been given in the lateral chest walls, the tissue was broken down and suppurating. There were râles in both lungs and the infant appeared feeble and shocked. The diarrhea had begun at age 7 days, the respiratory infection at 10 days. At age 16 days, when admitted, the diarrhea had ceased and the infant had had no stool for forty-eight hours. This was assumed to be due to atonic ileus because the diarrhea returned as soon as intravenous fluid was administered. The plasma carbon-dioxide combining power was 12.5 meq. per liter (28 volumes per cent). This infant was treated intravenously with 5 per cent glucose in physiologic saline, $\frac{1}{6}$ molar sodium lactate and plasma for a period of seventy-two hours. At this time 5 per cent rice gruel was given orally and was well tolerated. Five days after admission, 15 Gm. (0.5 ounce) of Nutramigen was added to the daily amount of rice gruel as a test feeding. This was gradually increased by small amounts to a level of caloric adequacy. The child was discharged in healthy condition at the age of 45 days weighing 3,300 Gm. (7 pounds, 4 ounces). The Nutramigen and rice gruel were continued at home. Some time later an attempt was made to replace the Nutramigen with whole homogenized milk. This caused the stools to become loose. The Nutramigen was resumed and the stools again became normal. Shortly afterward, by gradually adding homogenized milk and gradually decreasing the Nutramigen, the transfer was accomplished successfully.

RESULTS

The results in the entire series of seventy-five cases were as follows:

	NUMBER	RATE
Recovered	57	76 per cent
Died	18	24 per cent

The results in the patients fed with Nutramigen were as follows:

	NUMBER	RATE
Recovered	22	95.7 per cent
Died	1	4.3 per cent

FACTORS IN PROGNOSIS

1. *Virulence*: The factor of virulence is difficult of appraisal. Nelson and his co-workers^{2,3} had a much greater mortality rate in their second series than

*Mead Johnson and Company.

placed by milk in a gradual manner. We have seen not a few instances in which an abrupt change caused the diarrhea to recur.

SUMMARY

1. Seventy-five cases of epidemic diarrhea of the newborn were observed and treated during the period from July 26, 1944 to October 10, 1946. Twelve of these cases were acquired in the wards of our hospital from other patients infected with the disease. Some of this twelve were past the newborn period.

2. Hydration and correction of the acidosis were accomplished by intravenous and subcutaneous therapy with glucose, saline, and sodium lactate.

3. Oral feeding was commenced with small feedings of 5 per cent glucose in physiologic saline, followed by the feeding of a 5 per cent rice gruel.

4. Nutramigen was used as a beginning milk feeding in twenty-three cases, either with 5 per cent rice gruel or with boiled water.

5. The total mortality of the series was 24 per cent. The mortality of the cases fed with Nutramigen was 4.3 per cent.

6. Patients with relapsing or "biphasic" courses did not have an appreciably higher mortality than that of the series as a whole. Likewise, the severity of the acidosis at the time of admission had no direct bearing on the prognosis.

7. Low birth weight had a very definite influence in increasing the mortality.

8. We feel that Nutramigen is a very useful substance with which to resume the feeding of milk.

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	RECOVERED		DIED	
	NUMBER	RATE (PER CENT)	NUMBER	RATE (PER CENT)
Patients over birth weight	6	85.7	1	14.3
Patients at birth weight	5	50.0	5	50.0
Patients having lost 15 per cent or less	18	77.4	5	12.6
Patients having lost 16 per cent to 30 per cent	16	80.0	4	20.0

The five infants admitted at birth weight who died were all very small infants weighing respectively 908, 1,360, 1,360, 1,816 and 2,540 Gm. (2, 3, 3, 4, and 5.6 pounds). None had lost any weight when the diarrhea began.

There seems to be no correlation between loss of weight and mortality in this series.

DISCUSSION

We have attempted to predict the course of our cases by some measurable characteristic. The duration of the diarrhea prior to admission was not significant. In some cases active replacement therapy might have been delayed too long. In others a long pretreatment period might indicate that the infection was of low virulence or that the infant had or could develop ability to resist the infection. In the severest cases death occurs after a very brief period of illness and the disease is often not controlled by the accepted forms of treatment.

The occurrence of relapses did not appear to be significant in prognosis, as nearly three-fourths of the patients having these survived.

The severity of the acidosis appeared to reflect the amount of water loss rather than the virulence of the infection. Most of the infants with severe acidosis recovered. The severity of the weight loss, likewise reflecting the amount of water loss, cannot be correlated with the prognosis.

However, it seems very clear that small size at birth is a factor which makes the prognosis much more grave. However, Glynn⁴ reported 83 per cent of recoveries in his premature infants. Our poor results with these may reflect lack of facilities in the institutions referring these infants and the factor of exposure in transfer.

We are interested in the relation of resumption of milk feedings to the prognosis in these cases. Our data for infants whose milk feeding was resumed with Nutramigen were more favorable than those for the group as a whole. Inspection of the records shows that these infants were on the whole larger than those who did not receive it. Many of the Nutramigen fed infants were obviously very severely affected as judged by clinical appraisal. No clinical tetany has appeared in the postacidotic stage of these infants' cases: this may be due to the fact that Nutramigen contains a liberal amount of calcium gluconate (3.5 per cent). We have made no chemical determinations of the serum calcium, however, in these patients, to lend support to such a surmise.

It is our opinion that the Nutramigen should be continued in these cases until the danger of relapse is well past and that the Nutramigen should be re-

returning to normal. Pain in the right shoulder area disappeared after five days of treatment, and swelling resolved by the sixteenth hospital day. Repeat roentgenograms on the fifteenth hospital day revealed a circumscribed area of bony resorption, 1 cm. in diameter, at the metaphyseal end of the right humerus. Penicillin was discontinued on the nineteenth day. The patient was discharged in good condition after twenty-two days in the hospital. During the twenty-two months following discharge the infant had no further difficulty with the right arm. Follow-up x-ray examinations one week after discharge showed a circumscribed area of bone resorption similar to that seen two weeks earlier. Roentgenograms twenty-two months after discharge showed the right humerus to be normal.

CASE 2.—C. S., a 1-month-old Negro male infant, was admitted to the Gallinger Municipal Hospital on Oct. 4, 1946, because of swelling of the right leg of one day's duration.

One day before admission there was swelling of the right knee and lower two-thirds of the right thigh. This area was painful to touch. It was noted that the infant did not move the right leg for the twenty-four-hour period before admission. The family history was negative with the exception that the mother had been given a fifteen-day course of penicillin for the treatment of syphilis in the third month of pregnancy.

Physical Examination.—The temperature was normal on admission. The examination was normal with the exception of the right extremity. The right knee and lower thigh were moderately swollen, tender, and painful on motion. This thigh and knee were slightly warmer than the rest of the body.

Laboratory Data.—Hemogram showed 10,000 white blood cells of which 28 per cent were polymorphonuclears, 8 per cent eosinophiles, 1 per cent basophiles, 7 per cent monocytes, and 56 per cent lymphocytes. Three blood Kahn examinations were negative. On the first hospital day roentgenograms of the right femur were negative. (Fig. 1.)

Course.—A tentative diagnosis of acute osteomyelitis was made on admission. The patient was treated with 15,000 units of penicillin every three hours for ten days, a total of 1,200,000 units. There was no fever during the period of hospitalization. Three days after the beginning of treatment the infant could move his right leg. The redness and swelling of this leg gradually disappeared. X-rays taken at the end of treatment, on the fourteenth hospital day, showed destruction of the end of the right femur, with slight rarefaction of the shaft and a moderate amount of periostitis. Repeat films taken on the twenty-fifth hospital day and again one and one-half months after discharge showed definite healing. The patient's course from the time of discharge until the last clinic visit on Dec. 5, 1947 (a period of fifteen months) has been uneventful, and the infant has acted normally in all respects. X-ray examinations at eight and fifteen months after the onset of this disease showed the right femur to be normal in appearance. (Fig. 1.)

THE TREATMENT OF ACUTE HEMATOGENOUS OSTEOMYELITIS OF THE LONG BONES IN INFANTS AND CHILDREN

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DURING the past few years the treatment of acute hematogenous osteomyelitis has so changed that the management of this disease presents a problem which now is essentially medical rather than surgical. Thus, the pediatrician is now called upon to treat patients with osteomyelitis by coordinating the surgical, antibiotic, chemotherapeutic, and supportive measures to be employed. A review of the literature reveals relatively few reports on the treatment of osteomyelitis with penicillin, some of which are listed in the bibliography of this paper. Only one of these reports is published in a pediatric journal; namely, the report of Greengard¹ which deals with a general discussion and the treatment of acute hematogenous osteomyelitis in infancy. It is felt, therefore, that the report of some observations on the treatment of seven consecutive cases of acute osteomyelitis of the long bones in infants and children may be of value.

CASE REPORTS OF INFANTS

CASE 1.—R. T., a 5-month-old Negro male infant, was admitted to the Gallinger Municipal Hospital on Jan. 14, 1946, because of fever and paralysis of the right arm.

This patient had a history of a mild cold starting about two weeks before entry. Six days before admission it was noted that he had pain on movement of the right arm, and it seemed as though this arm were partially paralyzed. Fever was noted for approximately one day before admission to the hospital.

Physical Examination.—Temperature was 104° F., rectally on admission. The examination was normal with the exception of the right arm. It was noted that there was no voluntary movement of this arm and that passive movement caused pain. The right shoulder was moderately swollen and a fullness of the axilla was noted.

Laboratory Data.—Two blood cultures, a blood Kahn, and a tuberculin patch test, were negative. A blood count showed 10,600 leucocytes with 84 per cent polymorphonuclears and 16 per cent lymphocytes, and 9.5 Gm. of hemoglobin. Roentgenograms of the right humerus and clavicle were negative at the time of admission.

Course.—Penicillin, 20,000 units every three hours, was started on the day of admission. The temperature continued to be constantly elevated for four days and was of a septic type for two and one-half days more before

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returning to normal. Pain in the right shoulder area disappeared after five days of treatment, and swelling resolved by the sixteenth hospital day. Repeat roentgenograms on the fifteenth hospital day revealed a circumscribed area of bony resorption, 1 cm. in diameter, at the metaphyseal end of the right humerus. Penicillin was discontinued on the nineteenth day. The patient was discharged in good condition after twenty-two days in the hospital. During the twenty-two months following discharge the infant had no further difficulty with the right arm. Follow-up x-ray examinations one week after discharge showed a circumscribed area of bone resorption similar to that seen two weeks earlier. Roentgenograms twenty-two months after discharge showed the right humerus to be normal.

CASE 2.—C. S., a 1-month-old Negro male infant, was admitted to the Gallinger Municipal Hospital on Oct. 4, 1946, because of swelling of the right leg of one day's duration.

One day before admission there was swelling of the right knee and lower two-thirds of the right thigh. This area was painful to touch. It was noted that the infant did not move the right leg for the twenty-four-hour period before admission. The family history was negative with the exception that the mother had been given a fifteen-day course of penicillin for the treatment of syphilis in the third month of pregnancy.

Physical Examination.—The temperature was normal on admission. The examination was normal with the exception of the right extremity. The right knee and lower thigh were moderately swollen, tender, and painful on motion. This thigh and knee were slightly warmer than the rest of the body.

Laboratory Data.—Hemogram showed 10,000 white blood cells of which 28 per cent were polymorphonuclears, 8 per cent eosinophiles, 1 per cent basophiles, 7 per cent monocytes, and 56 per cent lymphocytes. Three blood Kahn examinations were negative. On the first hospital day roentgenograms of the right femur were negative. (Fig. 1.)

Course.—A tentative diagnosis of acute osteomyelitis was made on admission. The patient was treated with 15,000 units of penicillin every three hours for ten days, a total of 1,200,000 units. There was no fever during the period of hospitalization. Three days after the beginning of treatment the infant could move his right leg. The redness and swelling of this leg gradually disappeared. X-rays taken at the end of treatment, on the fourteenth hospital day, showed destruction of the end of the right femur, with slight rarefaction of the shaft and a moderate amount of periostitis. Repeat films taken on the twenty-fifth hospital day and again one and one-half months after discharge showed definite healing. The patient's course from the time of discharge until the last clinic visit on Dec. 5, 1947 (a period of fifteen months) has been uneventful, and the infant has acted normally in all respects. X-ray examinations at eight and fifteen months after the onset of this disease showed the right femur to be normal in appearance. (Fig. 1.)



Fig. 1—X-rays of the right femur, Case 2. *A*, Normal bone on admission. *B*, On the fourteenth day there was considerable destruction at the lower end of the femur with slight rarefaction of the shaft and moderate periostitis. *C*, On the twenty-fifth day there is definite healing. *D*, and *E*, One and one-half and fifteen months after onset. The bone is normal.

CASE REPORTS OF CHILDREN

CASE 3.—E. P., a 6-year-old Negro male child, was admitted to the Gallinger Municipal Hospital on Jan 2, 1945, because of painful, swollen left ankle.

This patient began to complain of pain in the left ankle three days before entry. At about this time it was noted that the left ankle was swollen and tender to touch. The patient's mother felt that he had fever for two days before admission to the hospital.

Physical Examination.—The temperature on admission was 104° F. (rectally). The examination was normal except for a moderate swelling, extreme tenderness, and pain over the left ankle.

Laboratory Data.—A blood culture, blood Kahn, and a tuberculin patch test were negative. The hemogram showed 58 per cent hemoglobin with 10,700 leucocytes per cubic millimeter. Roentgenograms of the left ankle area on the first hospital day were negative. On re-examination of this angle on the ninth hospital day, x-ray revealed a periostitis of the medial border of the lower one-third of the left tibia.

Course.—Sulfadiazine, 130 mg. per kilogram, and penicillin, 20,000 units every two hours, were started, respectively, on the day of admission and on the second hospital day. Under this treatment the swelling and pain gradually subsided so that by the eighth hospital day these findings were absent. Fever continued for the first four days in the hospital. The temperature then returned to normal. Penicillin dosage was reduced to 10,000 units every two hours on the sixth hospital day and continued for a total of twenty-three days. On the twelfth day after admission the temperature rose to 105° F. (rectally) and remained elevated for two days until sulfadiazine was discontinued. It was felt that the rise in fever probably was due to sulfadiazine sensitivity, but the subsequent administration of sulfadiazine from the twenty-first hospital day through the twenty-eighth day caused no rise in fever. On the nineteenth day after admission, and again on the thirty-eighth hospital day, x-rays revealed some increase in the previous periostitis with slight rarefaction of the distal end of the left tibia. The patient was discharged in good condition on the forty-fifth hospital day.

He was doing well when seen in the outpatient clinic one month after discharge. A repeat x-ray thirty-eight days after his release from the hospital (twelve weeks after onset) showed almost complete healing of the previously described osteitis and periostitis. The patient has moved from the city and has not been seen since the date of the last mentioned x-ray (April 6, 1945).

CASE 4.—M. J., a 7-year-old Negro girl, was admitted to the Gallinger Municipal Hospital on Feb. 7, 1945, because of pain in the right shoulder of two days' duration. The patient was perfectly well until two days before entry when she developed a pain in the right shoulder and, at about the same time, felt feverish. Swelling of the right shoulder was first noted on the day before admission.

Physical Examination.—The temperature was 102° F. (rectally) upon admission. The remainder of the examination was normal except for pain and moderate swelling over the right clavicle.

Laboratory Data.—A blood culture revealed the presence of *Staphylococcus albus* and *aureus*. A blood Kahn and a tuberculin patch test were negative. The blood count showed 11 Gm. hemoglobin per 100 c.e., and 25,000 leucocytes per cubic millimeter. On the tenth hospital day x-ray of the right clavicle showed no pathology. (Fig. 2.)

Course.—Sulfadiazine and penicillin, in dosage of 130 mg. per kilogram and 200,000 units per day by intramuscular drip, were started, respectively, on the day of admission and on the second hospital day. Under this treatment the fever ran a continued course for five days before returning to normal. The pain gradually lessened each day until by the seventh hospital day it had completely disappeared. Sulfadiazine was administered for fourteen days and then discontinued. Two weeks after entry 20 c.c. of pus were aspirated from a soft fluctuant mass that had appeared over the right clavicle. On the twenty-second hospital day the distal end of the right clavicle showed rarefaction and irregularity in its outline. On the thirty-fifth day after admission x-ray showed the presence of sequestra and some increased rarefaction. Penicillin was continued for twenty-seven days; the dosage being reduced, during the last week of its administration, to 5,000 units every three hours. The child was discharged in good condition on March 26, 1945, six weeks after entry.

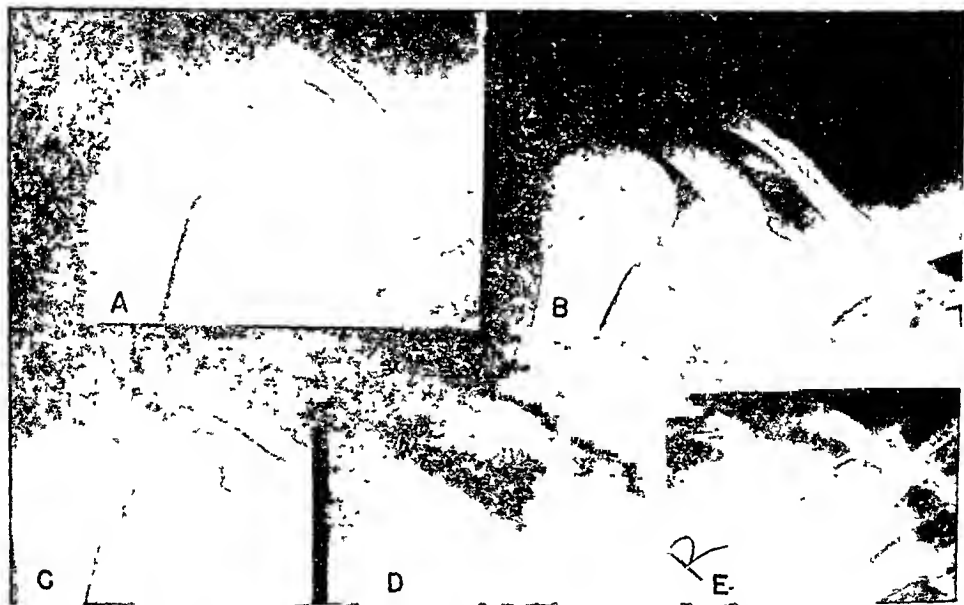


Fig. 2—X-rays of the right clavicle. Case 4. A, On the tenth hospital day the bone was normal. B, On the thirty-fifth day after admission there was diffuse rarefaction of the bone with some sequestration. C, Two months after admission there was continued increase in the bony destruction. D, Four months after entry there was some healing but a pathologic fracture was present. E, Thirty-three months after discharge the clavicle was essentially normal.

The patient was seen in the clinic on April 8, 1945, at which time there was continued increase in the bony destruction in the right clavicle. No further treatment was given and when she returned on June 11, 1945, four months after onset, the inflammatory lesion showed some healing, but there was a pathologic fracture at the site of the osteomyelitis.

The patient did not return for the treatment of this lesion, nor did she attend other clinics in the city. An examination in December, 1947, however, revealed that the patient had had no further difficulty since she was last seen,

and that there was no palpable difference between the right and left clavicles. X-ray examination thirty-three months after discharge (Dec. 16, 1947) showed the clavicle to be essentially normal, with no evidence of active bone disease.

CASE 5.—C. E., an 8-year-old Negro boy, was admitted to the Gallinger Municipal Hospital on March 9, 1945, because of pain in the left knee of one day's duration.

The patient had an upper respiratory infection for one week before entry with a fever as high as 103° F. during this interval. Two days before admission he struck his left knee with a piece of tin, and on the following day he noted that the left knee was painful. Pain in the knee remained until admission on March 9, 1945. The past history revealed a previous bout of acute osteomyelitis in the same site in June, 1943, which had resolved without surgery following the use of staphylococci antitoxin and sulfathiazole.

Physical Examination.—The temperature was 102° F. (rectally). The examination was otherwise normal with the exception of the lower portion of the left thigh, which was moderately swollen. Within this swollen area an extremely tender, small fluctuant mass was noted over the medial condyle of the left femur.

Laboratory Data.—Blood cultures were twice negative. A hemogram showed 13,400 leucocytes per cubic millimeter. The blood Kahn was negative. On the first hospital day x-ray of the left femur was negative.

Course.—Penicillin, in dosage of 10,000 units every two hours, and sulfadiazine were started on the day of admission. The temperature returned to normal after five days. Tenderness, pain, and swelling of the left lower thigh gradually lessened until all were absent on the eleventh hospital day. On the seventh hospital day a large area of rarefaction was noted in the distal metaphyseal end of the left femur. The same findings were present on repeat films made on the fifteenth day after admission. Sulfadiazine and penicillin were discontinued on the eighth and fifteenth hospital days, respectively. The patient was discharged with no complaints and with a negative physical examination on March 31, 1945, twenty-two days after admission.

This patient failed to return to the outpatient clinic as requested, but a re-examination in December, 1947, showed that he was perfectly well since discharge. X-ray examination thirty-three months after discharge (Dec. 11, 1947) showed the left femur to be entirely normal.

CASE 6.—P. B., a 4-year-old white boy, was admitted to the Gallinger Municipal Hospital on Dec. 7, 1946, because of vomiting and pain in the right leg.

Two days before entry it was noted that this child began to complain of pain in the right leg with inability to walk. Vomiting was also noted on this date. On the following day the fever became apparent.

Physical Examination.—The temperature was 104.8° F. The physical examination was essentially normal with the exception of the skin and the right leg. A few scattered petechiae were noted over the chest. The lower one-

half of the right thigh was moderately swollen and extremely tender to palpation. This area was also warmer than the rest of the body. Examination of the lower one-half of the right thigh gave the impression that a deep cellulitis might have existed because of a hard area deep in the central portion of the zone of tenderness and warmth.

Laboratory Data.—A blood culture revealed *Staph. aureus* to be present. The blood count showed 70 per cent hemoglobin with 14,650 leucocytes per cubic millimeter on admission. On the fourth hospital day roentgenograms of the right femur were negative.

Course.—Penicillin and sulfadiazine were started on the day of admission. Penicillin was given in doses of 20,000 units every three hours for one day and was then increased to 50,000 units every three hours. Sulfadiazine was given in dosage of 130 mg. per kilo per day. The temperature continued to be elevated for the first nine days' stay in the hospital, but from that time until discharge was normal. Penicillin and sulfadiazine were continued for the first twenty-three days after admission. The lower portion of the right thigh became somewhat fluctuant on the sixth day after treatment. Thereafter the swelling of the right femur gradually subsided until at the time of discharge, on the twenty-seventh hospital day, the swelling was almost absent. X-rays at this time showed definite periostitis and small areas of bone destruction in the distal metaphysis of the right femur. These changes were thought to be the normal evolution of a disease process controlled by penicillin.⁴

The patient had no complaints when seen on his first outpatient visit two weeks after discharge, and at this time the x-ray examination revealed increased periosteal reaction and increased osteitis at the distal metaphysis of the femur. This also was thought to be compatible with the normal resolution of the lesion. The patient did not return to the clinic again until March 28, 1947, almost four months after onset, when he was readmitted to the hospital because of pain in his right thigh. The history given at the time of the second admission revealed that the patient had done well until five days before the second admission when his right thigh was squeezed. From the time of this incident until he was readmitted on March 28, the patient had complained of pain in the right thigh. He had begun to walk with a limp. Examination at this time revealed moderate swelling and tenderness, particularly of the anterior and lateral aspects of the right thigh. The patient had a leucocyte count of 14,250 of which 74 per cent were polymorphonuclears, 24 per cent were lymphocytes, and 4 per cent were eosinophiles. A blood culture was negative. X-ray examination on the day of the second admission (March 28, 1947) showed marked periosteal thickening and both productive and destructive bone changes in the distal shaft of the right femur. Sequestra were also noted in this area.

Therapy during this second admission consisted of 50,000 units of penicillin every three hours for the first thirty-four days in the hospital. The course during this period of penicillin therapy, and until the forty-eighth hospital day (May 16, 1947) was uneventful. On this day he struck his right leg against the side of the crib with resultant pathologic fracture of the right femur. A

plaster spica was applied on the day following this fracture. The patient was discharged in a cast after sixty-one days in the hospital. After discharge following this second admission the patient has been seen in the outpatient clinic. His progress was satisfactory and by Aug. 27, 1947, he was walking without crutches. On this date a slight limp and slight muscle atrophy were noted on physical examination. He was seen again on Feb. 2, 1948. Repeat x-ray films made at that time showed anterolateral bowing at the site of the pathologic fracture, with marked sclerosis of the middle third of the bone. There was no evidence of active bone disease.

CASE 7.—H. D., a 7-year-old Negro boy, was admitted to the Gallinger Municipal Hospital on Aug. 16, 1947, because of pain in the left leg and fever of two days' duration. Three days before admission this patient struck his left leg on a step. Fever, swelling, and onset of pain in the left leg were noted two days before entry. These symptoms gradually increased in intensity until the time of admission.

Physical Examination.—The temperature was 102° F. (rectally). Examination was normal except for the lower left leg where, just proximal to the medial malleolus, a tender, warm, swollen area was noted.

H. D. N. M. AGE 6. ACUTE HEMATOGENOUS OSTEOMYELITIS.

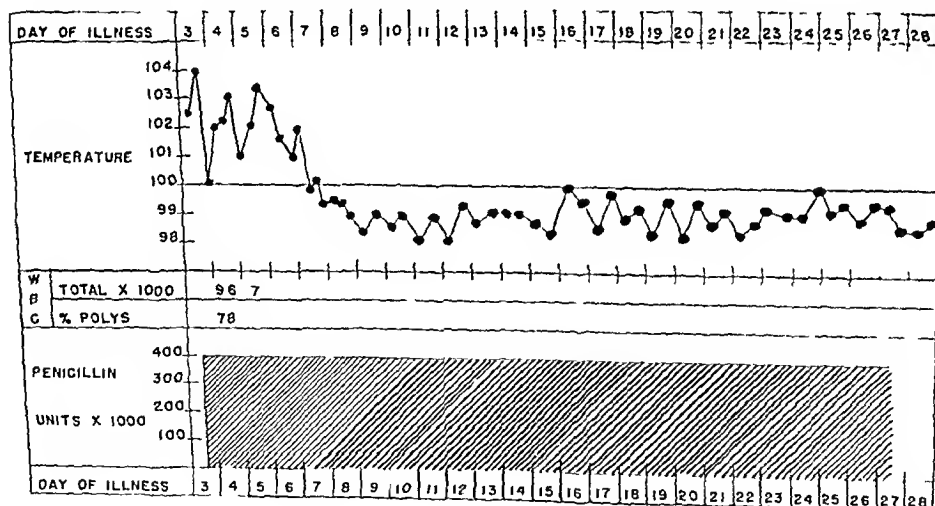


Fig. 3.—The clinical chart of H. D., Case 7.

Laboratory Data.—A blood Kahn was negative. The blood leucocytes numbered 8,600 with 80 per cent polymorphonuclear leucocytes, 18 per cent lymphocytes, and 2 per cent monocytes. The sedimentation rate was normal. Blood culture on two occasions was contaminated. A tuberculin patch test was negative. Roentgenograms of the left lower leg were negative on the second hospital day.

Course.—Penicillin was started on the day of admission in dosage of 50,000 units every three hours. Under this treatment the temperature remained elevated

between 100° and 104° F. (rectally) until the fourth hospital day, at which time it returned to normal. (Fig. 3.) Tenderness and pain of the lower left leg had almost disappeared by the third hospital day. The remainder of the course was uneventful. On the twentieth hospital day roentgenogram of the left tibia showed slight periostitis and some osteitis. Penicillin was discontinued after having been administered for twenty-four days. The patient was discharged completely asymptomatic on Sept. 12, 1947, twenty-seven days after entry.

The course after discharge was uneventful. No pain, tenderness, or swelling were noted after the patient left the hospital. X-ray follow-up studies on the eleventh day after discharge showed some recalcification of the previous area of osteitis at the distal metaphyseal end of the tibia. Walking was permitted at about this time. X-rays one and two months after discharge showed complete healing and disappearance of the osteitis and periostitis previously described. Five and one-half months after discharge there was a mottled appearance at the metaphyseal end of the left tibia, thought to be due to a sclerosis. Eight months after onset re-examination of the left ankle showed almost a complete clearing of the bone changes previously described in the distal end of the tibia. There was at that time no definite evidence of active bone disease.

DISCUSSION

The results of treatment with penicillin and sulfadiazine in acute hematogenous osteomyelitis in infants (both of our infant patients were less than 6 months of age) and in children are not comparable because of the natural difference in the course of this disease in these age groups. Green and Shannon,³ in their series of infants under 6 months, report a 44 per cent mortality rate. However, in those infants with acute osteomyelitis who survived, fairly rapid healing and eventual complete resolution of the bone was the rule, while sequestration and chronic draining osteomyelitis occurred infrequently. A quite different course occurs in chemotherapeutically and antibioticly untreated acute hematogenous osteomyelitis in young children. Green,² and Green and Shannon³ point out that this is due to differences in the osteolytic power of the usual infecting organism (a streptococcus occurs in 63 per cent of cases in infancy, and *Staph. aureus* occurs in 91 per cent of cases in children)²; the thinner, more vascular and spongier texture of the cortex of the infant's long bones; and lastly, because of the more loosely attached periosteum in infancy. In infants, all this favors the rupture of the bone abscess into the subperiosteal space and then, in turn, into the soft tissues.

The course of the two infants in our series shows the rapid resolution of the disease under penicillin therapy in dosage of 20,000 units every three hours for nineteen days in one instance, and a dosage of 15,000 units every three hours for ten days in the other case.

In the childhood group, four of the five patients had sulfadiazine in combination with penicillin. The dosage of penicillin was smaller (10,000 to 25,000 units every three hours) in the cases treated in 1945 than the dosage we now feel is optimal for the treatment of this disease. This was so largely because of

the difficulty of securing this drug. As can be seen, good results were obtained in all cases but one; namely, Case 6, (P. B.) in whom, in retrospect, it is felt that aspiration or open surgical drainage probably should have been carried out to evacuate the subperiosteal abscess. More prolonged administration of penicillin well may have benefited this patient also. The other cases required no surgical treatment of any nature with the exception of Case 4 (M. J.), in whom one aspiration of 20 c.c. of pus was made, and on whom no further procedures were employed, though immobilization of her fracture certainly was indicated.

These results, we feel, were in a good measure possible because penicillin therapy alone or in combination with sulfadiazine was started early in the course of the disease in all patients. Thus, it is essential that the doctor who is responsible for the care of infants and children have, at all times, a high degree of suspicion for the presence of this disease. For this reason we are giving a brief outline of the diagnostic points and conditions to be differentiated: All infants or children who are presented with the picture of pain, protective movements of an extremity, heat and swelling of the painful extremity, and localized tenderness of such areas should be investigated carefully for the presence of acute hematogenous osteomyelitis. The diagnosis is primarily a clinical one for, as is well known, bone changes visible by x-ray do not occur for at least seven to fourteen days. If this interval for bone changes is awaited before therapy is started, the period of medical treatment will have escaped and the condition will be one in which surgical intervention will be almost inevitable. Conditions that must be considered and differentiated from acute osteomyelitis are acute arthritis, cellulitis, scurvy, syphilis, thrombophlebitis, poliomyelitis, and rheumatic fever. If these conditions cannot be differentiated conclusively from osteomyelitis, it is preferable that they be treated unnecessarily with penicillin, rather than that possible osteomyelitis go untreated.

TREATMENT

The excellent results obtained in six of these seven cases reported, and the experiences of Altmeier,⁴ Altmeier and Helmsworth,⁵ McCorkle, Silvani, Stern and Warmer,⁶ and Compere, Schnute, and Cattell⁸ show that surgery can be avoided, mortality lowered to almost the vanishing point, and the patient adequately treated by medical means.

Altmeier⁴ and Altmeier and Helmsworth,⁵ in their excellent articles on this subject, have shown that the results of penicillin therapy are dependent upon early adequate treatment. It can be stated generally that the amount of bone destruction and the necessity for surgery are related directly to the number of days' delay in instituting penicillin therapy. Other factors to be considered, however, are the virulence and sensitivity of the organism, the extent of area involved, the adequacy of therapy, and the age of the patient. Altmeier and Helmsworth⁵ have reported the following time relationship to treatment and results: If treatment is begun within the first two to three days of illness, prompt recovery usually results without resort to surgery. Rarely, under these circumstances, will a small subperiosteal or deep abscess require drainage. (Our

Cases 4 and 6 are examples of the exceptions.) If proper therapy is delayed to between four and seven days from the time of onset, the likelihood of surgical drainage (aspiration or incision) is increased and sequestration occasionally develops. Delay beyond seven days usually results in marked bone destruction, requiring not only medical therapy but also major surgery for drainage of abscesses and removal of sequestra.

It is evident that the best results in treating acute hematogenous osteomyelitis are obtained in those cases in which treatment is started during the first two to three days of the disease. Thus, in order to avoid delay, treatment should be initiated even when the diagnosis may be somewhat in doubt. This therapy should be continued until acute osteomyelitis is ruled out as a diagnostic possibility. Examples of such a situation are the several cases of deep cellulitis in which we could not completely eliminate osteomyelitis as a diagnostic possibility, and in which penicillin was continued until the clinical course and x-ray studies pointed to the absence of bone infection. We have seen at least one case in which another possibility exists; the clinical course was typical of acute osteomyelitis but x-ray changes never occurred to confirm the diagnosis. It is possible that early therapy so limited the gross bony changes that they were not extensive enough to be seen by x-ray. Similar experience has been noted by Higgins, Browne, and Bodian⁹ and Altemeier and Helmsworth.⁵

The use of sulfonamides in the treatment of acute osteomyelitis has been of considerable value, but the addition of penicillin to our therapeutic armamentarium has greatly improved the prognosis of this disease. Mathews and Hutter¹⁰ have reported the results of sixteen cases of acute osteomyelitis treated with sulfonamides as compared to nine cases treated with penicillin and sulfonamide. They gained the definite impression that the penicillin-sulfonamide series had the least severe bone lesions. It was noted that 90 per cent of the sulfonamide series had surgical intervention as compared to but 20 per cent (two patients required aspiration) in the penicillin group. The majority of our patients had sulfadiazine and penicillin, but we now feel that penicillin alone in adequate dosage probably will be sufficient. We have no definite evidence to show that sulfadiazine has not added to the effectiveness of the therapy. However, the results of others^{4, 5, 6} and the results with three of our patients show that penicillin alone, when used early, is an excellent agent for the treatment of acute osteomyelitis.

The dosage of penicillin to be used in the treatment of acute hematogenous osteomyelitis in infants and children is very important. Reasonably good results have been obtained when doses varying from 10,000 to 24,000 units every two or three hours have been employed. Surgical intervention has been necessary in several patients who have been treated with this dosage schedule, however,^{6, 7} and it is our impression that with these doses, the course has been more protracted than might be necessary. In order to attempt to reduce the occasions for surgery and to speed up the recovery, we are now using a dosage schedule of 50,000 units of penicillin every three hours for from two to four weeks or more. We feel that penicillin in maximal doses should be given for at least two

weeks and never less than one week after the temperature is normal and the symptoms have subsided. If the infection seems to be severe and bone destruction appears to be extensive, the administration of penicillin probably should be continued for longer periods, even up to four or six weeks. We are not certain that infants require as heavy dosage of penicillin as do older children, but we have gained the clinical impression that infants require almost equal amounts of the drug as do older children or young adults in the treatment of the same disease.

Based upon our experiences with these seven cases of this disease, and upon a review of available literature, we are now using the following general plan for care of acute osteomyelitis. This plan has been developed as we have gained experience with the "medical handling" of this disease and as penicillin has become more available.

1. The treatment of osteomyelitis is started in all cases at the earliest possible moment when a tentative diagnosis is made, or when some other diagnosis, such as cellulitis, seems likely but osteomyelitis cannot be ruled out completely.

2. Supportive care for dehydration and pain, and other symptomatic therapy are given as the condition may indicate.

3. Penicillin is administered in dosage of 50,000 units every three hours intramuscularly for fourteen to twenty-eight days or more.

4. Orthopedic consultation is obtained in all cases, but generally the care is chiefly medical unless deep abscesses are present. Such abscesses, when present, are aspirated or drained. If the disease is of moderate duration (six to seven days), there is a great probability that surgical care will play the major role, with penicillin being an essential aid but not effective as a sole agent.

5. Our patients are not treated by plaster immobilization, for it is felt that ordinary rest in bed is adequate splinting in all cases in which only medical care is necessary. Those in which deep abscesses are present or in which extensive bone involvement are noted because of delay in diagnosis, or because of a particularly massive and virulent infection, are splinted under the direction of the orthopedic consultant.

6. Weight-bearing is not permitted until x-ray studies show regression of bone lesions. Roentgen examinations are recommended every one to two weeks until the bone changes are showing regression, and then every four to eight weeks until complete healing. After complete healing, the patient should be followed every six months to a year for several years by x-ray studies.

SUMMARY

1. A report of seven consecutive cases of acute hematogenous osteomyelitis is given.

2. The importance of having a high degree of suspicion for the presence of this disease, and the early initiation of adequate treatment on only a clinical diagnosis are stressed.

3. A suggested outline for the medical treatment of acute osteomyelitis is given.

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DWARFISM OF UNDETERMINED ETIOLOGY

A STUDY OF BIRTH WEIGHT AND SUBSEQUENT DEVELOPMENT

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THIS study was carried out on a series of dwarfed children selected from the case records of the Children's Hospital in Boston. Various indices of growth and development were calculated and compared with each other as well as with the birth weights.

Case Selection.—Since the term infantilism is commonly used synonymously with dwarfism,¹ all the cases indexed under both classifications at the Children's Hospital in Boston were consulted. As indicated in Table I, certain cases were excluded from the series. For example, not only a definite diagnosis of hypothyroidism but also suggestive clinical evidence was sufficient to omit the patient from the study. There remained forty proportionate dwarfs in whom no cause for dwarfism was implicated. With similar criteria, the diagnosis of pituitary dwarfism is often made.² The cases selected were seen at the Children's Hospital from 1919 to the present and included both ward and clinic patients

TABLE I. SELECTION OF CASES

Total number of cases indexed as dwarfism		56
Cases used	31	
Cases not used	25	
Hypothyroidism	9	
Insufficient data	7	
Malnutrition	3	
Renal disease	1	
Rickets	1	
Achondroplasia	1	
Celiac disease	1	
Severe scoliosis	1	
Record unobtainable	1	
Total number of cases indexed as infantilism		28
Cases used	9	
Cases not used	19	
Insufficient data	6	
Renal rickets	4	
Records unobtainable	3	
Malnutrition	2	
Tuberculosis	1	
Disproportion	1	
Above normal stature	1	
Incorrectly indexed	1	

Data Used.—The cases used were those in which both height and weight measurements were recorded; in many there were multiple sets of observations

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but the study of individual growth curves was not done. In all the calculations performed in this paper only the first applicable set of observations was used, thus avoiding the weighting of the results by having more than one observation for each case in any particular correlation. A summary of the information used is given in Table II.

TABLE II. SUMMARY OF CASES

CASE	SEX	BIRTH WEIGHT (LB.)	CHRONOLOGIC AGE (YR.)	HEIGHT (IN.)	WEIGHT (LB.)	BONE AGE* (YR.)
1	M	7.50	10.2	43.4	38.0	—
2	M	6.10	5.2	37.5	28.5	4.5
3	F	5.00	7.0	38.0	30.0	3.0
4	F	7.40	5.1	39.0	28.0	4.3
5	M	—	5.4	37.8	27.8	—
6	F	6.80	5.8	39.0	34.0	—
7	F	5.00	1.6	27.0	15.0	—
8	F	6.50	6.3	41.8	33.3	5.0
			4.6	34.5	26.3	—
			5.6	37.5	31.0	3.7
9	M	—	7.8	37.9	30.3	—
10	M	8.12	4.6	38.0	33.3	—
11	F	7.00	6.8	35.0	28.0	2.0
12	F	5.75	3.8	36.0	21.9	—
13	F	5.50	4.1	36.8	24.5	—
14	M	7.00	4.8	35.5	27.8	3.0
15	F	7.00	6.1	40.8	30.3	5.8
16	M	3.00	4.4	37.0	24.8	2.0
17	M	9.50	7.4	41.0	38.3	—
18	F	1.50	1.7	25.5	11.5	—
19	F	4.20	7.0	38.0	23.3	4.0
20	M	7.60	0.9	27.0	18.5	—
			5.1	35.8	27.0	2.0
21	F	7.44	4.5	31.5	23.5	0.2
22	F	13.00?	3.2	30.3	17.1	—
23	F	5.00	1.6	31.5	19.5	—
			1.8	32.4	19.4	1.0
24	M	9.00	8.8	41.5	30.0	3.5
25	F	8.09	9.2	43.8	46.8	9.0
26	F	6.25	5.8	36.0	24.3	2.5
27	F	4.50	3.2	30.5	16.0	2.0
28	F	6.00	4.3	37.8	28.5	3.8
29	F	—	2.1	32.8	21.0	—
30	F	7.00	0.8	26.0	13.4	—
31	M	—	6.7	42.0	37.5	4.3
32	M	4.90	2.3	33.5	22.0	1.3
33	F	7.50	7.8	40.5	30.0	3.6
34	M	7.00	9.5	45.0	57.3	—
35	M	—	9.0	41.5	41.5	7.3
36	M	5.75	2.4	30.3	21.3	—
37	M	10.25	10.8	48.8	54.5	8.0
38	M	—	9.0	43.0	43.0	—
			12.8	48.5	51.5	8.8
39	M	8.25	6.9	37.0	29.0	5.0
40	F	6.00	6.9	39.5	31.8	3.3

*When given as a range, the midpoint was taken.

There were not sufficient data to allow study of birth length, race, family background, mental age, dental development, glucose tolerance tests or 17-ketosteroid excretion. Similarly, therapy was instituted in only a small number of cases and then chiefly for diagnostic purposes and with no significant height changes.

Over three-fourths of the children were brought in with a chief complaint related to retarded development.

Standards of Dwarfism.—To compare the heights of the children in this series with various standards for dwarfism, Fig. 1 was constructed. This shows a normal mean height curve⁴ and the several lower limits of normal calculated therefrom. The heights observed in the dwarf series are indicated also. It is apparent that the standard for dwarfism of 70 per cent of the mean height of coevals⁵ is extreme in relation to the cases studied. The upper limit of these cases corresponds most closely to the standard of height at 80 per cent of chronologic age,⁵ i.e., a child would be considered a dwarf if his height were less than the normal height at 80 per cent of his age. The wide variation of these standards is worthy of note.

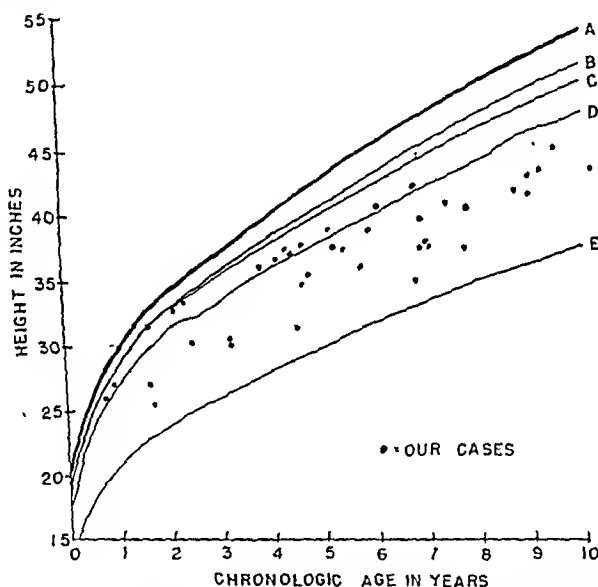


Fig. 1.—Comparison of several standards of dwarfism with cases studied.*

A, Normal mean height

B, 10 percentile

C, Normal mean height at 80 per cent of chronologic age

D, Mean height - 3 S. D.

E, 70 per cent of mean height

The normal mean height[†], A, the 10 percentile, B, and the standard deviation used to calculate standard D[‡], are from Vickers and Stuart's values for normal children⁴. Standard C[§] and standard E^{||} were both derived from the values of A.

*These standards were calculated for boys; up to 10 years of age the growth curves for boys and girls almost coincide.

†For ages under 2 years, the height values are for measurements taken with the patient in the recumbent position.

Sex Distribution.—There were eighteen males and twenty-two females—not a significant difference—which were not considered separately in any subsequent calculations or figures.

Skull X-ray Findings.—Twenty-two of the cases had one or more skull x-rays taken. All cases so examined had negative findings.* Thus no positive x-ray evidence of pituitary pathology was observed in the group.

*One case showed questionable sellar enlargement, but was considered negative on a subsequent x-ray examination 1.3 years later.

Comparison of Mean Dwarf Birth Weight With Normal Birth Weight.—

The birth weights of those in the series were compared with those of normal children. To obtain standards more comparable to the data at hand, it was decided to calculate a normal birth weight. This was done in the following manner. The mean birth year of the dwarf series was 1931; consequently the records of the Boston Lying-in Hospital for that year were consulted. A total of 117 birth weights were selected from consecutive cases about equally distributed in January, April, July, and October. This was done to compensate for normal seasonal variations in birth weights.⁷ The dwarf series showed no significant monthly variation in frequency. Newborn infants not surviving their stay in the Lying-in Hospital were excluded from the normal series, as all the dwarf cases had obviously survived at least this length of time. Premature babies were not excluded provided they had filled the foregoing requirements. The Boston Lying-in Hospital records utilized were for non-private cases which strengthens their socioeconomic similarity to the group of dwarfs. The findings relative to the dwarf and normal birth weights are summarized in Table III.⁸ There is no apparent reason why the group for which the birth weights were available (34 of the 40) should have any higher or lower mean birth weight than the dwarf group as a whole.

The difference between the birth weights of the normal children and the dwarfs is highly significant. Using other normal birth weights as standards^{4, 9} gave a similar degree of significance. This makes the group of dwarfs unlike the usual concept of pituitary dwarfs who are generally stated to have normal birth weights.^{3, 9}

TABLE III. BIRTH WEIGHT

	DWARF SERIES	NORMAL SERIES
Mean (lb.)	6.46	7.54
Standard deviation (lb.)	1.76	1.10
Number of cases	33	117
Critical ratio	3.3	
Probability	0.1 per cent	

Calculation of Growth Indices.—Using the height and weight standards given by Jackson and Kelly,^{10†} the height and weight ages were calculated for the dwarf group. The height age of an individual is the age for which his height is normal. The weight age was derived in a similar manner. The bone ages were taken from the clinical records and had been estimated from hand and wrist bone x-rays. The developmental ages were derived from the Wetzell Grid.¹¹

An index of height development was formed by means of the following formula, height age/chronologic age \times 100. A weight index was similarly calculated, weight age/chronologic age \times 100, as were a skeletal index, bone

⁸One birth weight value was omitted from the dwarf series. This was for a child claimed to be 13 pounds at birth but who only weighed 17.1 pounds at 3.2 years of age (Case 22). This birth weight value was marked with a question in the clinical record.

[†]It will be noted that the normals used here are different than those used in Fig. 1. Vickers and Stuart's data⁴ only covered children through 10 years of age while Jackson and Kelly's standards⁹ did not include values for both Standard Deviation and 10 percentile.

age/chronologic age $\times 100$, and a developmental index, developmental age/chronologic age $\times 100$. These four indices are measures of retardation; the values lying farthest below the normal of 100 are most retarded. Further as a measure of relative thinness, an index consisting of weight age/height age $\times 100$ was calculated.⁵

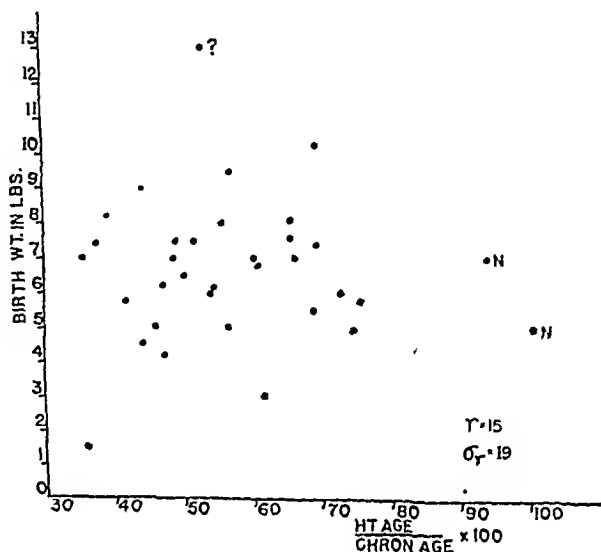


Fig. 2.—The value of r given was calculated leaving out the values of the point marked "??" (Case 22, previously mentioned in the text) and the two points marked with "N" (Cases 23 and 30, whose height age/chronologic age $\times 100$ was greater than 80). Their inclusion would not have increased the value of the correlation coefficient, r .

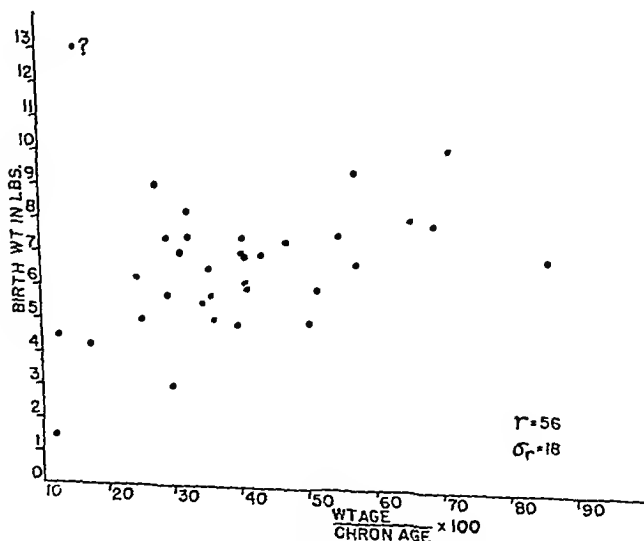


Fig. 3.—The point marked with "??" (Case 22) was not used in calculating the correlation coefficient, r .

Correlation of Growth Indices.—The results of the correlation coefficients which were calculated are shown on the respective figures. The correlations utilized the indices described above. By having ages in both numerator and denominator it was hoped to avoid certain fallacies involved in correlating two variables each of which is dependent on time.

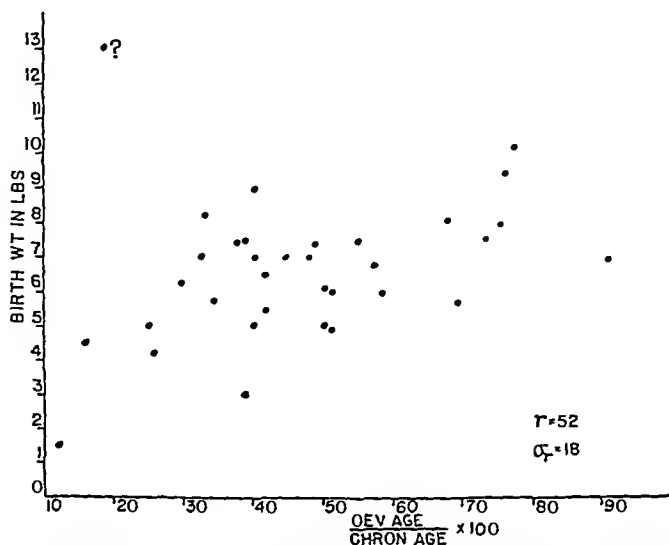


Fig. 4.—The point marked with “?” (Case 22) was not used in calculating the correlation coefficient, r .

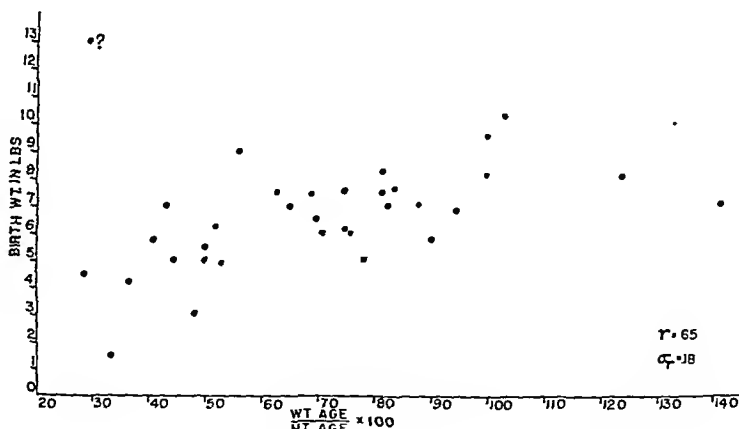


Fig. 5.—The point marked with “?” (Case 22) was not used in calculating the correlation coefficient, r .

No significant relationship was found between birth weight and subsequent height retardation (Fig. 2).

The weight retardation (Fig. 3) and developmental retardation (Fig. 4) were each directly related to the smallness of the birth weight by about the same extent. This might be expected, in view of the fact that the developmental age is so largely dependent on weight.

The correlation of birth weight with future thinness (Fig. 5) was slightly greater.

The children selected as dwarfs were of short stature (Fig. 1). As mentioned above, it was found that the dwarf group had a mean birth weight

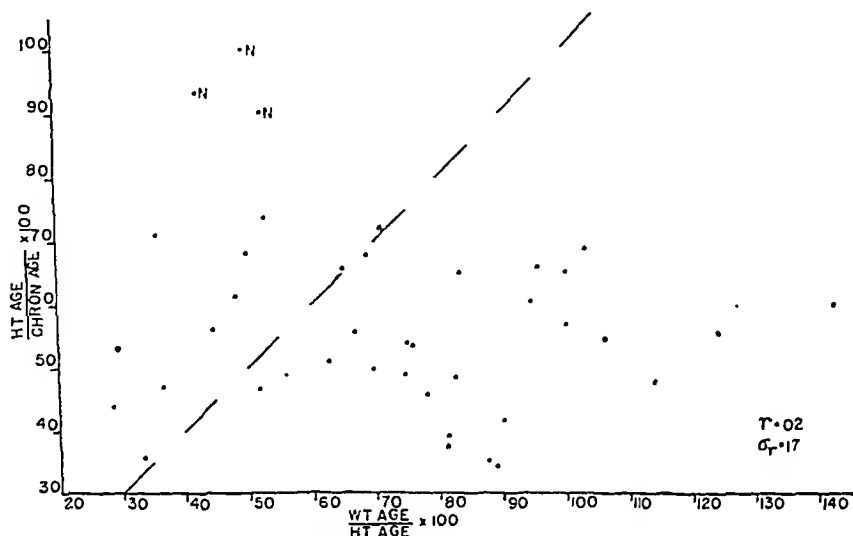


Fig. 6.—The three cases marked with "N" (Cases 23, 29, 30) were not used in the computation of the correlation coefficient, r . Their inclusion would not have increased the value of r . The broken diagonal line represents the points at which the coordinates have equal values.

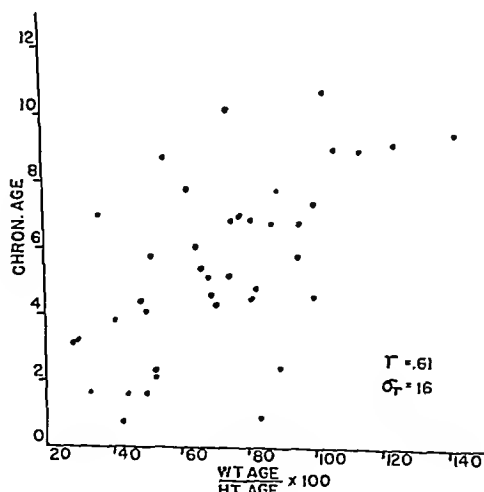


Fig. 7.

below normal (Table III). On the basis of these two findings one might have expected the shorter dwarfs to have been smaller at birth, but such was not the case (Fig. 2). An explanation of the findings may lie in the fact that as a group the dwarfs were thin and this thinness was related to the smallness

at birth (Fig. 5). The same family background leading to a poor diet in pregnancy and hence a low birth weight¹² may also have prevailed during the dwarfs' home life and so resulted in thinness.

It was found that the extent of height retardation and thinness were unrelated in the dwarf group (Fig. 6). If malnutrition had played a very large role in causing the diminished stature, and if the thinness index is a measure of malnutrition, one might have expected some correlation in Fig. 6.

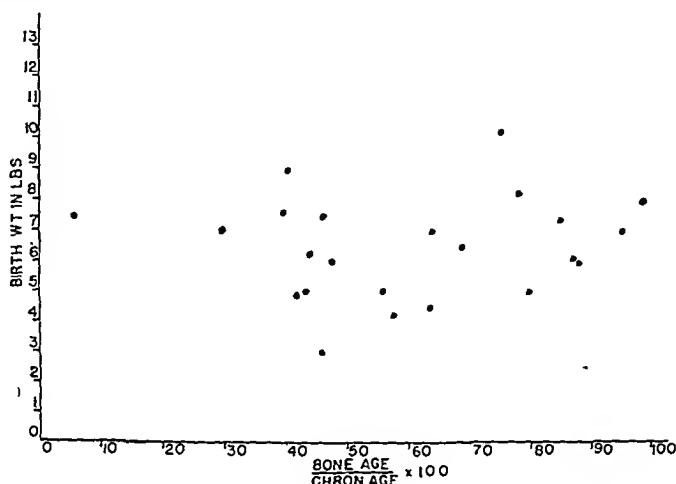


Fig. 8.

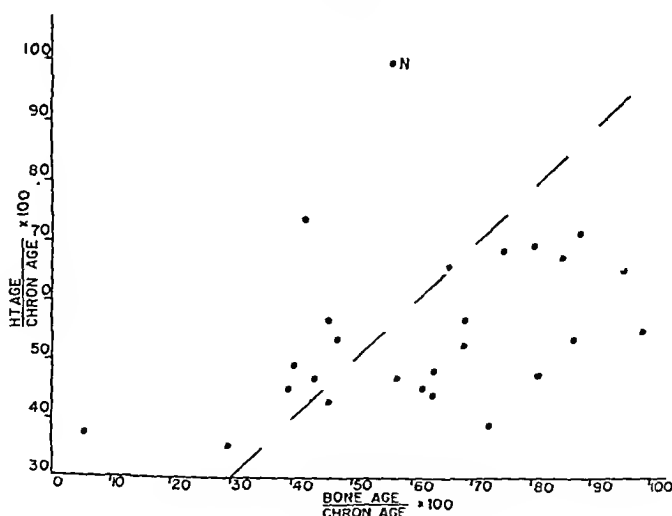


Fig. 9—The broken diagonal line represents the points at which the coordinates have equal values.

It was shown that there was a distinct tendency for the younger dwarfs to be thinner (Fig. 7). Aside from explaining this by some intrinsic developmental pattern, one should consider the possibility that in younger children mothers are more likely to note and become concerned over weight retardation than

height retardation. No striking associations were found between bone age retardation and birth weight (Fig. 8), height retardation (Fig. 9), or developmental retardation (Fig. 10). It was noted, however, that the developmental age retardation in general exceeded the bone age retardation. A difference in normals used for the Wetzel Grid and for the bone age standards could cause this picture.

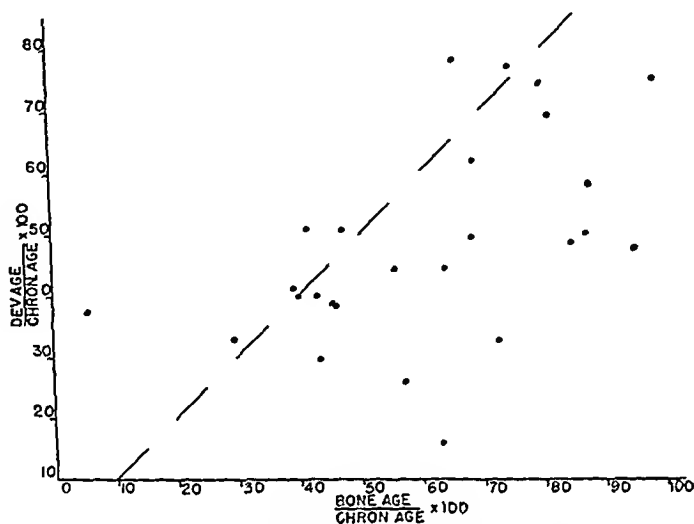


Fig. 10.—The broken diagonal line represents the points at which the coordinates have equal values.

SUMMARY

A series of forty proportionate dwarfs from the files of the Children's Hospital in Boston in whom no cause for diminished stature had been found was studied. The following conclusions were reached.

1. The most satisfactory standard of dwarfism for the series appears to be height age/chronologic age $\times 100$ equal to 80 or less.
2. The mean birth weight of the series of dwarfs was 1.1 pounds below that of a series of comparable normal children.
3. The degree of height retardation was not related to the birth weight.
4. The weight and developmental retardation were correlated positively to birth weight.
5. There was a positive correlation between birth weight and subsequent thinness.
6. There was, however, no correlation between thinness and height retardation.
7. The degree of thinness was correlated positively to the age when first seen.

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TENSION TYPE OF CONGENITAL PULMONARY CYST

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THE large single tension type of congenital pulmonary cyst is quite rare. It usually occurs in infants and until the last decade almost always resulted in a fatality. However, with the realization that this lesion can be successfully handled surgically, these cysts have become of exceptional interest to the pediatrician, roentgenologist, and the surgeon. We are reporting the successful removal of such a cyst in a 4-month-old infant.

No attempt has been made to review the entire literature but in this country interest in this disease was stimulated by Koontz¹ in 1925. He reviewed the literature and reported on 108 cases of congenital cysts of the lung. In seven of these cases there were large single cysts present while in the remainder the cysts were small and usually multiple. Koontz at the time of his report felt that the case he was reporting was the first of its type in the American literature; however, he found out at a later date that Pappenheimer had reported such a case in 1912. In 1933 Anspach and Wolman² wrote an excellent paper on this disease. They found on a review of the literature 150 cases of congenital lung cysts and they state "only a few of these were in infants and in fewer still was the condition diagnosed and its course watched during life. In most instances the lesion was an accidental finding at necropsy." In 1936 Oughterson and Taffel³ published a review of the subject and a case report in which an 8-year-old boy, with five independent cysts was treated surgically by converting the five cysts into a single cyst. This cyst was then treated by continuous negative pressure through a catheter until it sealed off. The boy had remained well with no evidence of recurrence for two years following surgery. In 1943 Fischer, Tropea, and Bailey⁴ reported the first successful pulmonary resection, lobectomy upper and middle lobes, for congenital cystic disease in an infant. In 1946 Gross⁵ published a case in which he had done a successful pneumonectomy on a one-month-old infant with the same diagnosis. In his article Gross discussed the therapeutic approach to this problem and listed four methods of value for relief of respiratory embarrassment.

1. Introduction of needle into cyst as a temporary lifesaving procedure.
2. Introduction of trocar followed by catheter into cyst for prolonged aspiration. This may be useful in collapsing cyst in preparation for surgery.
3. Marsupialization of the cyst onto the chest wall with methods of destruction of the lining membrane. This method may be used in the single cyst.
4. Enucleation of the cyst or removal of pulmonary tissue containing it. This he regarded as the treatment of choice.

Burnett and Caswell⁶ in 1948 reported a successful lobectomy for pulmonary cysts in a 15-day-old infant who had been explored through the abdomen one day previously, with the mistaken diagnosis of a congenital diaphragmatic hernia. In this case a needle was introduced into the cyst without relief of symptoms following the abdominal exploration.

CASE REPORT

The family history is of interest. The mother and father are Rh positive. Their serology is negative. There have been five pregnancies. The first resulted in a miscarriage at four months. The second miscarried at four and one-half months. The third was a full-term stillborn infant. The fourth was a full-term infant who died twelve hours after delivery. Unfortunately, no post-mortem examinations were carried out.



A.



B.

Fig. 1.—A, Retouched posteroanterior film to show initial size of cyst. B, Lateral film showing anterior position of cyst.

W. B. was a full-term white male infant born Aug. 17, 1947, weighing 7 pounds, 10½ ounces. Following delivery there was no difficulty although the mother states the child always seemed to breathe rapidly. However, on Dec. 14, 1947, there was a marked change and respirations became rapid and labored. On Dec. 16, 1947, he was admitted to the Miami Valley Hospital with rapid, gasping respirations and his color had changed to a grayish blue. Physical examination revealed a well-developed male infant weighing 12 pounds, 6 ounces, in acute respiratory distress. Rectal temperature on admission was 101.2° F. and four hours later 101.4° F. Respirations were gasping and rapid, approximately 60 per minute. The pulse rate was 160 per minute. The right thorax appeared larger than the left. The percussion note was hyperresonant over the right thorax and breath sounds were absent. There was slight dullness at the left apex with normal breath sounds over the left thorax, except at the left base where numerous inspiratory râles were heard. The heart sounds were distant and rapid and could best be heard just to the left of the left nipple. The remainder of the examination was essentially normal except for moderate abdominal distention.

Roentgenologic study showed a large, air-containing sac filling the major portion of the right thorax (Fig. 1). Atelectatic compressed lung was present at the right apex and at the right base. There was dense clouding at the left apex which appeared to be contiguous

with the mediastinum. A lateral film showed the air sac to lie principally in the anterior position. The diagnosis of a cyst of the lung was made by Dr. George Nicoll, the roentgenologist.

Course in Hospital.—A 20-gauge needle using Novocain anesthesia was immediately introduced into the cyst through the fifth interspace just lateral to the right nipple. There was

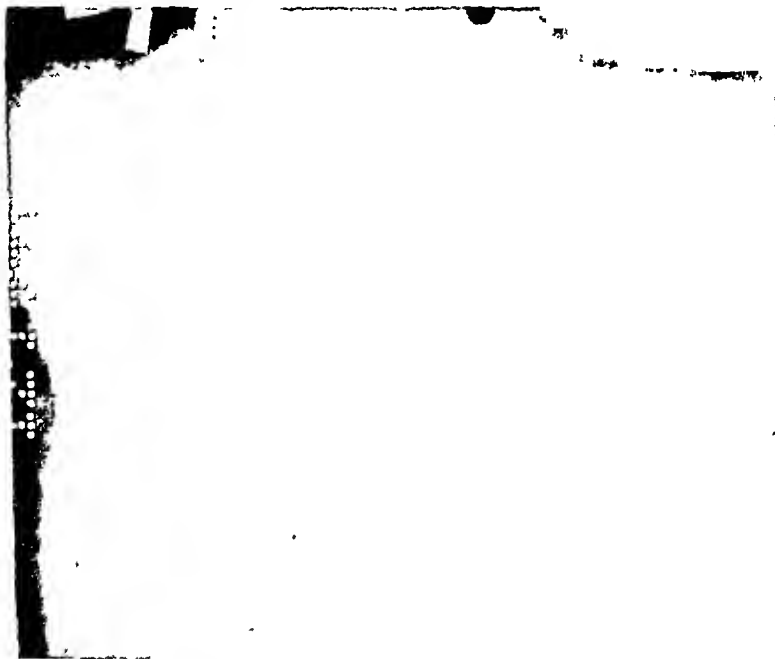


Fig. 2.—Collapse of cyst after introduction of needle.

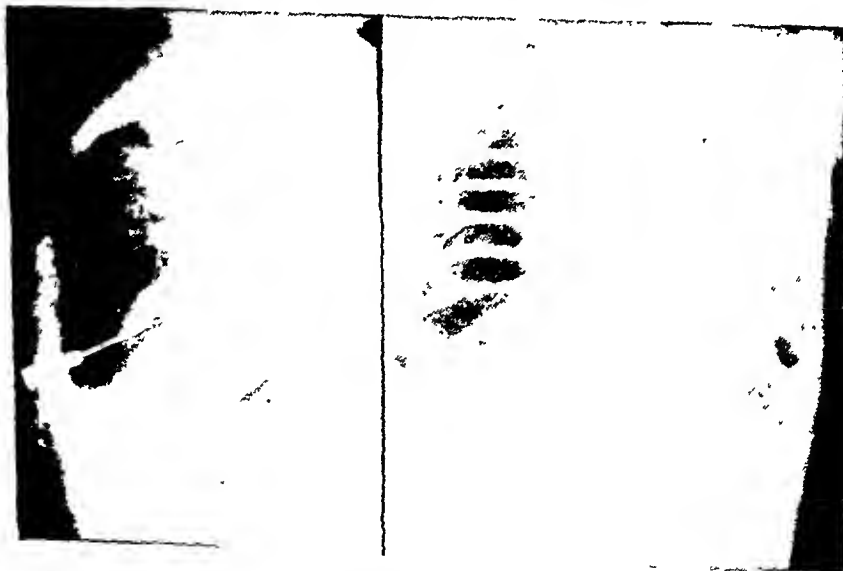


Fig. 3.—Re-expansion of cyst with needle in situ is shown in both posteroanterior and lateral films.

an immediate gush of air from the needle, and the needle was fixed in place with adhesive straps and connected to a tube. The distal end of the tube was placed underwater in a bottle. There was immediate improvement and respirations became less rapid and labored and the cyanosis disappeared. There was a steady bubbling of air into the water bottle with each respiration. The child was started on penicillin 20,000 units every 3 hours. The following day due to the fact that a moderate amount of air had leaked into the subcutaneous tissue, it was decided to introduce a catheter into the cyst. Under Novocain anesthesia a trocar was introduced through the same interspace and a catheter was placed to a depth of approximately 4 to 5 cm. Following this there was a constant flow of air through the catheter into the water bottle. However, checkup x-ray films the next day showed the catheter to be lying along the wall of the cyst and not in it. Later that day air stopped coming through the catheter and the child became dyspneic and cyanotic. The catheter was removed, and a needle was reinserted into the cyst. On two occasions during the next five days, it was necessary to change the position of the needle due to the fact that the flow of air stopped. This immediately caused the development of both dyspnea and cyanosis in the infant. By the fifth hospital day the child's temperature which had been peaking to 101° F. daily returned to normal and his general condition was improving steadily. His appetite increased and the abdominal distention which had been present had disappeared. On the tenth hospital day surgery was carried out.



Fig. 4.—Posteroanterior film four months after surgery showing shift of mediastinum back toward midline.

Operative Procedure.—The anesthesia was positive pressure endotracheal using both cyclopropane and ether; it was administered by Dr. John Valin. A cannula was inserted into the left saphenous vein just above the ankle and sutured in place. The infant was given 200 c.c. of blood during the operation.

The right thorax was prepared and draped and a right anterior incision from approximately one inch lateral to the sternum to the midaxillary line was made. The anterior portion of the sixth rib was resected subperiosteally. The thickness of the periosteum was striking. On opening the pleura the cyst bulged through the operative wound so that it was hardly necessary to use any retraction. The cyst occupied the entire right middle lobe and was intimately attached to both upper and lower lobes which were markedly compressed and

atelectatic. The cyst was opened and its wall was moderately thick. There were two bronchioles lying on the inner surface from which a steady stream of air escaped. One was situated just below the attachment to the upper lobe and one on the anterior wall approximately 1.5 cm. above the lower lobe. The cyst extended over to the left of the sternum. It was dissected free from the upper and lower lobes by the clamp-and-cut method. No true fissures were present between the cyst and the upper and lower lobes. Dissection was carried down to the hilum. A fairly good sized artery and vein leading to the cyst were present. These were from a division of the pulmonary vessels to the left lower lobe and were ligated and divided just above the point where they branched. No separate and distinct middle lobe bronchus could be identified. The cyst wall was intimately adherent to the upper lobe vessels which were displaced to the left beneath the sternum and it was decided to leave a small portion of the cyst in situ at this point. Interrupted silk sutures were used throughout except where the upper and lower lobes had been divided from the cyst. Here a running atraumatic 0000 chromic catgut suture was used. A small Pezzar catheter was placed into the right pleural cavity through a stab wound in the midaxillary line. Both the upper and lower lobes expanded well under positive pressure anesthesia and the wound was closed using interrupted silk sutures for the pleura, the periosteum, the muscle layer, and the skin. After closure all remaining air in the thorax was aspirated through the catheter, and the catheter was connected to a rubber drainage tube whose distal end was underwater.



Fig. 5.—Photograph of child two months after surgery.

Postoperative Course.—Following this operation the child was given 100 c.c. of blood during the afternoon. He was started on water, 2 ounces, eight hours after surgery, and the following morning was started on a restricted formula, 3 ounces every four hours. This was gradually increased. For the first forty-eight hours there was quite marked abdominal distention, but he had a stool following a tap water enema on the first postoperative day. Thereafter distention subsided and he had daily stools. He was kept in an oxygen tent until the third postoperative day. His temperature spiked to a maximum of 103.4° F. by rectum on the second day and then gradually declined reaching a normal level on the sixth day and remaining normal thereafter. The leucocyte count reached a peak of 25,600 with 65 segmented and 21 immature cells on the second day and declined steadily until the seventh day when the white blood cell count was 11,150 with 38 segmented and 19 immature cells. An x-ray of the chest on the third day showed the right upper and lower lobes to be expanding well with no appreciable amount of fluid in the thorax. The catheter drained sero-sanguineous fluid, between 100 and 200 c.c., for the first twenty-four hours and by the third day the to-and-fro movement of water in the tube had stopped, indicating the catheter had become sealed off. It was removed the following day. He was given penicillin 20,000 units every 3 hours intramuscularly and sulfadiazine orally $2\frac{1}{2}$ grains every four hours through

the seventh postoperative day. A chest film on the tenth day showed the upper and lower lobes of the right lung to be completely expanded with some shift of the mediastinum and heart back toward the midline. He was discharged home on the twelfth day.

Pathologic Report.—(Melvin Oosting, M.D.) The specimen consists of an irregular piece of tissue measuring 10 cm. in length and $\frac{1}{2}$ mm. in thickness. It is fibrous in character with small pieces of lung tissue attached.

Microscopic examination shows the wall to be lined with a respiratory type of epithelium on a basis of fibrous connective tissue and smooth muscle. There are occasional islands of cartilage present and a number of well-defined bronchioles and bronchi. One side of the wall is covered by pleura showing areas of relatively recent nonpyogenic inflammatory reaction. On another part of the wall islands of collapsed and aerated alveoli may be seen. Some of these contain recent hemorrhage with large phagocytes containing blood pigment. This has the appearance of a congenital cyst of the lung.

Subsequent Course.—This infant has had an uneventful follow-up with no respiratory difficulty for six months following surgery. Roentgenograms at two and four months showed complete expansion of the right upper and lower lobes with farther shift of the mediastinum toward the midline.

DISCUSSION

The so-called congenital tension cyst of the lung is simply a bronchiogenic cyst arising in pulmonary tissue. These cysts arise due to an abnormality in the development of the bronchial tree. They may arise within lung tissue or adjacent to it if the continuity of the bronchial tree is maintained. However, it is quite common for a mass of cells to be completely pinched off during embryologic development and in this case a cyst may be completely separate from the bronchial structures. This is a fairly frequent occurrence and explains the development of bronchiogenic cysts in the mediastinum. These congenital cysts all have a common histologic appearance. They are lined by ciliated columnar epithelium with smooth muscle and elastic tissue in the wall. Cartilage is frequently present as well as mucous secreting glands. In contrast, the inflammatory cyst has simply a fibrous tissue lining, but often there may be a superimposed inner layer consisting of inflammatory cells and macrophages. If marked infection has occurred within a congenital cyst causing destruction of the lining membrane and of the cyst wall, then the diagnosis of whether a cyst is of congenital or of inflammatory origin is difficult.

Congenital cysts are usually quite small, containing mucoid secretion. They may cause no symptoms and remain quiescent. However, occasionally one may encounter a tension cyst which develops rapidly and causes marked respiratory embarrassment. The cause for the sudden enlargement is obscure. It is best explained by a ball valve type of mechanism in which air can enter the cyst but cannot escape as rapidly as it enters. This may be due to a twisting of a bronchus or bronchiole or to edema which partially occludes the lumen so that the egress of air is impeded. In this case at operation there were two definite small bronchi present. Their course was long and tortuous and it was easy to see how the outflow of air might be partially or totally blocked. The reason why this type of cyst is found primarily in infants is due in all probability to the elasticity and pliability of the pulmonary tissue which allows for rapid expansion of the cyst within the lung and concurrently the cyst as it increases in size is allowed by the mobility of the mediastinum to push over into the opposite thorax.

The differential diagnosis must include congenital diaphragmatic hernia, emphysematous blebs of the lung, and tension pneumothorax. The first is ruled out by the administration of barium by mouth. The air-filled loops of bowel in the thoracic cavity will fill with the opaque medium and the diagnosis will be made. Anspach and Wolman² in 1933 pointed out how a congenital diaphragmatic hernia might simulate congenital cysts, and they recommended the use of oral barium to avoid such a mistake at that time. Emphysematous blebs of the lung at times may be difficult to differentiate, but usually they are thin walled and on the pleural surface, and the diagnosis can be readily made. Tension pneumothorax can be diagnosed quite easily by the roentgenogram. Once the diagnosis of a tension cyst has been made, with signs and symptoms of respiratory embarrassment present, immediate therapy aimed to relieve the tension in the cyst is in order. This may be done in one of several ways, either by decompression with a needle or catheter or by immediate surgical intervention. It is our feeling that with the large tension type of cyst, needle or catheter decompression should be the first step. This may well be a lifesaving procedure. There are certain dangers in both needle and tube decompression of such a cyst. It is possible for air to leak into the pleural cavity, thus causing a tension pneumothorax. This might be fatal and the infant must be watched closely for this. In our case a subcutaneous emphysema developed due to air leaking into the subcutaneous tissue about the needle. This was not serious and was relieved by a change of position of the needle to stop the leak. On one occasion a trocar followed by a catheter was introduced into what we thought was the cyst. There was a constant bubbling of air into the water bottle to which the catheter was attached, but an x-ray the following day showed the catheter to be lying along the wall of the cyst between it and the parietal pleura. The air was leaking out of the cyst through the trocar hole and the catheter was not in the cyst proper. On two occasions while the cyst was being decompressed there was a recurrence of dyspnea and cyanosis. Each time we were warned that this was going to develop, as the continuous flow of air into the water bottle had stopped. The cause for this was an obvious block at the end of the needle. The marked increase in pressure within the cyst, when this occurred, was well illustrated by the fact that when we changed the position of the needle, the plunger of a 10 c.c. syringe which was attached to it was blown out of the barrel onto the floor. These complications are not serious if attended to promptly, but we mention them to show the associated dangers of decompression and to stress that these infants need close supervision. It is undoubtedly safer to decompress with a small mushroom type of catheter which has been well fixed, than a needle, if the catheter has been placed in proper position initially. With proper decompression it is possible to relieve both respiratory and circulatory embarrassment and to return the physiology of the chest to a more normal state. At the same time a pneumonitis which may be associated with a compression atelectasis can be treated by chemotherapy and if need be the infant can receive blood, electrolytes, proteins, etc., so that the patient becomes a good surgical risk rather than a poor one. After this has been accomplished, we feel removal of the cyst is indicated. Infants and children tolerate pulmonary surgery well. Partial

pulmonary resection, lobectomy, or even pneumonectomy are much easier procedures in an infant than in an adult. The vascular and bronchial trees may be dissected out with ease and the structures readily identified. The hilar structures are thin and pliable and there is not the fixation and fibrosis that one usually finds in the adult due to an old inflammatory process. We wish to stress that the surgeon should not have a rigid plan of operative procedure before opening the chest, but this should be flexible as the operative findings may change the entire procedure. For example in our case we were not sure whether or not a pneumonectomy would be necessary (see Fig. 1). Instead, it was possible to enucleate the cyst almost completely except for a small portion which was left overlying the vessels to the upper lobe. It might be said that since the cyst occupied the entire right middle lobe, we actually carried out a lobectomy. The point is equivocal since very little if any normal pulmonary tissue was removed. The upper and lower lobes which were markedly atelectatic expanded well under positive pressure anesthesia after the removal of the cyst and on the third postoperative day, x-ray examination showed them to be almost completely expanded. It is our feeling that to conserve normal pulmonary tissue is always worth while when the success of the surgical procedure is not jeopardized by so doing. We fully realize that at times it may be necessary to sacrifice an entire lung, but this should be determined only after careful operative examination. This infant has now been followed for six months. Roentgenograms of the chest taken two months after surgery showed complete expansion of the right upper and lower lobes, with a shift of the heart and mediastinal structures back toward the midline. An x-ray at four months showed even farther shift toward the midline. The mediastinal structures are still displaced slightly to the left, but we feel that in a short time they will be back in their normal position. The child has been completely free from any respiratory difficulty since surgery.

CONCLUSION

1. Congenital tension cysts of the lung in infants are amenable to surgery.
2. Decompression of the cyst by needle or catheter may be a lifesaving procedure.
3. With decompression of the cyst and supportive therapy the surgical risk may be changed from bad to good.
4. Removal of the cyst either by enucleation or by excision of pulmonary tissue containing it is the treatment of choice.

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ACNE NEONATORUM

REPORT OF ACNE VULGARIS IN TWO INFANTS

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INFANTILE acne is of interest not only to pediatricians but also to dermatologists and endocrinologists because the presence of its lesions raises the question, not as yet satisfactorily answered, of its causation: whether the active role is to be attributed to hormones or to some extraneous factor or factors. As against the acceptors of the theory of hormonal causation, its opponents assume that the sebaceous glands are more or less dormant in infantile life, that they do not become active until puberty, and, therefore, that they are incapable of a causative role in any difficulty of an earlier age. On the other hand, followers of the "hormone school" believe that hormonal influence exists soon after birth and so may be a cause of acne among infants, although it should be explained that its effects are to be understood as derived from the mother and as the result of her pregnancy. Wiener¹ in his excellent text remarks: "The comedones and false milia, i.e., the false enlarged sebaceous glands and the sometimes observed acne of the newborn (also his vigorous lanugo growth) have often been interpreted as hormonal pregnancy reaction." He further states: "One has even, in view of the numerous gonadal stimulations, spoken of a 'miniature puberty.'" Nor is Wiener alone in this conception of the etiology of acne vulgaris in infants, for Jaquet and Rondeau² too regard the sebaceous glands as active but in a secondary phase deriving from hormonal factors in the mother. As against this position, others like Kraus³ regard the hormonal effect as "not proved" since they see the common blood circulation during pregnancy as without any special significance in this particular.

However, it is clear that acne vulgaris exists among infants. Leiner⁴ remarks upon his observation of many cases of true acne, not milia: These are cases of acne punctata among infants and children ranging from 3 to 12 months in age. In accounting for this, Sulzberger and his colleagues⁵ join with the majority group of writers already cited in attributing acne to the stimulation of the pilosebaceous apparatus by hormones at that time when the maternal and therefrom, probably, the fetal circulation, contain the highest index of hormones, e. g. prolans and estrins. Ordinarily, according to these same writers, this activity ceases at birth and is not resumed until puberty when the individual attains his own sex hormones. Further, their belief that the stimulation of the pilosebaceous apparatus depends directly or indirectly on the hormones, helps to explain the acne vulgaris of adolescence. Belisario⁶ may be mentioned among others who believe that infant acne is somehow related to hormonal influence. The present writer himself has inclined to the hormonal theory and

it is his conviction that in the two cases of *acne vulgaris* of which this paper treats, hormones provide the etiologic background. For example, in connection with them there persisted for several weeks as a concomitant feature a mastitis neonatorum, a fairly common condition which is generally interpreted as indicating that gonads are at work, and which may be explained as resulting from the transfer of hormones from the mother to the infant via the placenta. It is reasonable to believe that such a transaction may at once engorge the breasts of newborn infants and stimulate the quiescent sebaceous glands, with acne resulting. As Belisario⁶ writes, reporting a case of infant acne from Australia: "The general belief now appears to be that some form of imbalance of the endocrine glands, in particular as it is evidenced by exacerbation around the menstrual cycle, plays a leading part in the etiology of acne." On the other hand, various extrinsic factors have been held accountable for acne in infants, among them the indiscriminate use of oils and ointments, the use of camphorated oil, and the rubbing of the child's face with a shawl. Slavens⁷ sponsors the theory that occlusion of the facial glands by oils and ointments is responsible for the formation of comedones and subsequently for acneiform eruptions. Both Dore⁸ and MacLeod⁹ indict the local use of camphorated oil as playing a definite etiologic role in the cases coming under their observation, while Harries¹⁰ reports at least one case in which trauma, produced seemingly by the presence of a shawl, caused acne. Leiner⁴ points out a more general causative relationship, observing that most of the infants he saw showed weakness and ill-health. Crocker¹¹ believes that the etiology of infantile acne is different from that of postpuberty, and considers warmth and moisture as combined etiologic factors in infant acne. He cites for evidence the case of a 3-year-old girl who was treated for a laryngeal obstruction with repeated linseed poultices and whose back and lower chest thereafter presented scattered comedones mingled with acne papules and pustules. However, the force of this observation is somewhat reduced by his admission that a bacterial factor too may have operated. To most observers also a sex difference appears, male infants apparently being affected more often than female infants.

CASE REPORTS

CASE 1.—The mother of C. P., a white male infant who was seen when he was one week old, noticed soon after birth that his cheeks were blotchy. A week later numerous milia appeared upon the skin of the forehead and of both cheeks and were followed by blackheads. At this time too several small pustules were noticed upon the right side of the face and forehead. Until the age of 3 weeks the infant was fed exclusively upon breast milk when a simple dilution of evaporated milk and water with milk sugar was added. The mother was enjoying good health; she denied taking any medication including bromides and iodides. For cleansing only pure olive oil and castile soap and water were used upon the infant. When first he was seen, the infant exhibited engorged breasts, which subsided spontaneously after ten days; otherwise, the physical examination was negative. An ointment (3 per cent of precipitated

sulphur in zinc ointment U.S.P.) was prescribed after the use of resoreinol (1 per cent in 70 per cent alcohol) failed to bring about improvement. The lesions had entirely disappeared six weeks after the patient was first seen. Thereafter monthly checkups failed to show any return of the acne. At the age of 9 months the infant was happy and in good health upon the sort of diet indicated for that particular age. Only a small scar upon the right cheek marked the site of one of the pustules.



Fig. 1.—Case 1, C. P., a male infant. Photograph taken at 10 weeks of age. A, Note papules and comedones upon both cheeks and forehead. B, Profile. Note comedones and pustules upon right cheek, also pustule above right eyebrow.

CASE 2.—A female infant of Italian parentage was first seen at the age of 3 months at the Skin and Cancer Hospital in Philadelphia. The lesions consisted of papules and comedones upon the skin of the forehead, cheeks, and chin. The mother first noticed the "pimples" upon both cheeks when the infant was 4 days old; and these were followed in the same locality by black-heads a month later. There were no other lesions. The patient was a full-term, bottle-fed infant who had received no medication containing bromides or iodides, nor had iodized salt been used in the preparation of her food. As in the former case, inquiry revealed, that a few days after birth the infant's breasts had become enlarged and had remained engorged for almost three weeks. Physical examination was negative. There was a hemoglobin of 75 per cent; red blood cells, 3,900,000 per centimeter; white blood cells, 7,900; polymorphonuclear leucocytes, 53 per cent; monocytes, 1 per cent; lymphocytes, 46 per cent. The blood sedimentation was 8 mm. in one hour (Wester-

gren). Therapy consisted of the use of soap and water followed by the local application of the official *lotio alba*, N.F. one-quarter strength, but this worked no improvement. Then a lotion (2 per cent resorcinol in 70 per cent alcohol, U.S.P.) was prescribed for application three times daily, again without effect. For a third prescription, 3 per cent precipitated sulphur in zinc oxide ointment, U.S.P., was ordered and an almost immediate improvement followed its use. The infant was seen again four months after her first visit to the hospital and at that time her skin was perfectly free of acne.



Fig 2—Case 2, M. A. S., a female infant. Photograph taken at 3 months of age. Note papules and comedones upon both cheeks, chin, and forehead.

SUMMARY

1. Two infants, one male, aged one week, the other female, aged 3 months, both presented typical lesions of acne vulgaris.

2. These cases and other cases among infants reported in the literature seem to indicate that acne vulgaris is not so uncommon among newborn infants as has hitherto been believed. Careful examination of the skin of the newborn infant would probably reveal the presence of papules, pustules, and comedones in a much greater frequency than that in which they have been assumed to occur.

3. The mastitis neonatorum concomitant with or preceding the acne vulgaris suggests the correctness of the preponderant opinion that infantile acne is dependent upon the gonads and results from stimulation of the sebaceous glands.

4. The use of a topical ointment containing 3 per cent of precipitated sulfur in a zinc oxide base resulted in a prompt improvement of the lesions.

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INCIDENCE OF DISEASES AMONG READING FAILURES AND NONFAILURES .

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SOME children of normal or superior intelligence fail to learn to read, even when exposed to teaching that is adequate for the majority of children. The condition is usually called, "reading difficulty," although other terms include, "alexia, word-blindness, reading disability, and strephosymbolia." Sometimes such cases are subdivided into functional and organic groups, the latter being referred to as having "specific reading disability." This implies the presence of some lesion which results in weakness of the language function, accompanied, according to some, by lateral dominance variations.

Reading difficulty exhibits an hereditary tendency and occurs more frequently in boys than in girls. Almost no pathologic studies of the brains of reading difficulty cases have been reported. Hinshelwood¹ is credited with a single necropsy. This appears to have contributed to his conclusion that a lesion in the left supramarginal and angular gyri in a right-handed person might cause reading failure. However, much more recently Orton² pointed out the fact that no pathologic condition of the visual memory center had been demonstrated up to that time.

A great deal of investigation of possible causes of reading failure has been carried on, but it has not been as productive as one could wish because of the variation in the preparation for research and the background of the investigators. For example, physical studies have been made by physicians, psychologists, optometrists, teachers, and others, using all kinds of techniques ranging from the conventional to the bizarre. It is no wonder that there has been so little agreement between them. Sometimes relatively comparable data have been interpreted quite differently by investigators with different backgrounds and divergent points of view. Out of the great mass of studies one major fact has emerged. There is no single cause of reading failure. Each case presents a constellation of etiological factors, varying from person to person and including such things as physical, emotional, psychological, social, and pedagogic components.

The present study was made in order to contribute somewhat to the understanding of the part played by physical factors in reading difficulty cases. Eight hundred seventy-five reading failures were compared with 486 nonfailures as to the frequency of various groups of diseases and defects. The median age of the reading failure group was 9 years, 7 months, while that of the control group was 11 years, 7 months. The median intelligence quotient of the reading failures was 102, while the controls presented a median of 103. The records of each child were studied, the defects and diseases were tabulated, and the frequency

of each was calculated. In the statistical material that follows, the word "diseases" includes diseases and defects except as noted.

It was found that the reading failure group exhibited 21.1 per cent more frequent disease than did the control group. This supports a similar trend noted in an earlier study.³ When the various classes of diseases were considered separately, smaller differences were displayed, but there was a general tendency for the reading failures to exhibit the higher frequency. Speech defects and diseases of the mouth, nose, throat, and ears (exclusive of dental conditions) displayed the greatest differences, while diseases of the eyes (exclusive of eye defects), diseases of the circulatory system, and diseases of the urogenital system exhibited medium differences between the groups. Table I presents the complete tabulation by classes of disease, while Table II lists the various diseases encountered in each.

TABLE I. COMPARISON OF FREQUENCIES OF DISEASES OR DEFECTS AMONG READING FAILURE AND NONFAILURE GROUPS

DISEASE GROUP	READING FAILURE (%)	NONFAILURE (%)	DIFFERENCE (%)
Total disease	36.1	15.0	21.1
Malnutrition	0.2	0.0	0.2
Deficiency diseases	1.4	2.0	-0.6
Alimentary tract	0.3	0.2	0.1
Mouth, nose, throat, and ears	7.8	3.2	4.6
Lungs	0.4	0.0	0.4
Circulatory system	2.5	0.4	2.1
Blood and blood-forming organs	1.1	1.6	-0.5
Endocrines	2.6	1.6	1.0
Bones and joints	0.0	0.0	0.0
Urogenital system	2.6	0.4	2.2
Skin	0.1	0.0	0.1
Allergy	1.2	0.6	0.6
Nervous system	2.2	1.2	1.0
Specific infectious diseases	0.4	0.0	0.4
Speech defect	6.2	1.2	5.0
Eye diseases	4.7	2.6	2.1

A previous study⁴ involving 1,000 reading failures, including the cases used in the present investigation, reported differences in the frequencies of predominantly ocular factors; visual acuity, amblyopia, refraction, muscular imbalance, fusion, lateral dominance in terms of eyedness and handedness, and the speeds of word and object perception. It showed that hypermetropia of one diopter (D.) or more, exophoria of 6 or more prism diopters at the reading distance, and retarded speed of word perception occurred over 10 per cent more frequently among the reading failures. The differences in frequencies between the reading failure and control groups were considerably higher than in the frequencies of the physical conditions reported in the present study. For example, hypermetropia of one diopter or more occurred 30 per cent more frequently among the poor readers, while exophoria of 6 or more prism diopters at the reading distance occurred 11 per cent more frequently in the same group. The reading failures also exhibited 24 per cent more frequent retardation in the speed of word perception.

TABLE II. DISEASES ENCOUNTERED IN READING FAILURE AND NONFAILURE GROUPS

DISEASE GROUP	READING FAILURES	NONFAILURES
Nutrition	Malnutrition Celiac disease	None
Deficiency diseases	Avitaminosis	Avitaminosis
Alimentary tract	Colitis Megacolon	Megacolon colon
Mouth, nose, throat and ears	Deviated septum Nasal obstruction Enlarged uvula Diseased tonsils Sinusitis Perforated eardrum Granulations in nasopharynx	Diseased tonsils Deviated septum Sinusitis
Lungs	Tuberculosis Empyema	None
Circulatory system	Cardiac disease Patent ductus arteriosus	Rheumatic heart Patent ductus arteriosus
Blood and blood-forming organs	Purpura Anemia	Anemia
Endocrine	Hyperthyroidism Hypothyroidism Diabetes Fröhlich syndrome	Hyperthyroidism Hypothyroidism Diabetes
Bones and joints	Spina bifida Osteitis deformans Clubfoot Deformities of second finger and toes Deformities of arms Bifid terminal phalanx	None
Urogenital system	Undescended testis Absence of left testis Kidney disease Enuresis Diabetes insipidus	Enuresis
Skin	Alopecia areata	None
Allergy	Unspecified	Unspecified
Nervous system	Anesthesia of toes Birth palsy Bell's palsy Brachial palsy Epilepsy Facial ties Hydrocephalus Paralysis left leg Parkinson's syndrome Postconcussive state Rathke pouch cyst Trauma (brain)	Birth palsy Facial ties Migraine
Specific infectious diseases	Chorea Syphilis	None
Speech defects	Unspecified	Unspecified
Eye diseases	Amsocoria Cataract Choked disc Corneal scar Chalazion Chorioretinitis Deformity of left pupil Fixed left pupil Hordeolum Hole in macula Nystagmus Ptosis Neoplasm Persistent hyaloid artery Color blindness Occlusion of tear duct	Cataract Chronic conjunctivitis Coloboma Nystagmus Opaque nerve fibers Retinitis Retrolbulbar neuritis

Although the results of the present comparison show a greater frequency of disease among the reading failures as compared with nonfailures, the differences in frequency in individual diseases is not great in relation to the whole group. When one considers the proportion by which the frequency is higher in the reading failure group than in the control group, it is noted that the diseases of the urogenital system and of the eirenulatory system are each more than six times as frequent among the reading failures, speech defects more than five times, and diseases of the mouth, nose, throat, and ears, and allergy more than twice those of the control group. Furthermore, certain conditions encountered among the reading failures were not met at all in the control group. These included malnutrition, diseases of the lungs, diseases of the bones and joints, diseases of the skin, and specific infectious diseases.

Clinically it is well known that certain diseases often interfere with learning and are important in that connection when they occur. For example the improvement in schoolwork, including reading, is usually prompt when a hypothyroid child is treated successfully. Therefore, the fact that a disease occurs more or less infrequently in large groups of reading failures should not lead one to ignore it as a possible handicap to learning.

Treatment of reading difficulty cases falls into two main divisions. First, any unfavorable physical conditions which might reduce the child's ability to compete physically or mentally with others of his own age should be corrected or treated. It then becomes the job of the teacher to instruct the child up to the limit of his ability to learn to read. In recent years education has developed many efficient techniques for remedial teaching in the field of reading. They include a large number of new approaches in addition to the old and cumbersome alphabet, phonic, and kinesthetic methods. At present there are some remedial schools, especially in the larger centers. Many private and public schools maintain a reading specialist who is trained in remedial teaching; other schools, having no one appointed for this particular job, maintain one or more teachers who have taken special work in remedial reading instruction and who are able to devote part of their time to such work. Some localities have none of these facilities and find it necessary to fall back on the summer school or camp which offers remedial teaching, the private remedial reading teacher, or individual instruction by a well-trained grade-school teacher.

SUMMARY

Diseases or defects were found to be 21.1 per cent more frequent among 875 children who were failing in reading than among 486 children who were successful in learning to read. The different classes of diseases encountered and the treatment of reading failure are discussed briefly.

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Case Reports

BONE FORMATION IN SKIN AND MUSCLE: A LOCALIZED TISSUE MALFORMATION OR HETEROTOPIA

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THE formation of mature, well-developed bone within human skin, subcutaneous tissue, and muscle is an occurrence as striking as it is rare. To the three cases reported in the literature as occurring in children, we wish to add a fourth.

CASE REPORT FROM CHILDREN'S ORTHOPEDIC HOSPITAL

A white female infant was born prematurely on April 8, 1944, weighing 3 pounds, 15 ounces. The parents were 26 and 30 years old. There was one sister aged 5 years. The family history was irrelevant. The baby was kept in an incubator for one month and did well on Olac formula. She received vitamin supplements in correct amount and variety and developed in normal sequence. Immunizations were given for diphtheria, pertussis, and variola. Illnesses included occasional respiratory infections and scarlatina without sequelae.

When the infant was removed from the incubator at the age of one month, a small, hard, irregular area was noted near the left breast. On advice of a physician, the baby was put in sunlight a few minutes each day for a week. The skin along the radial aspect of the left arm thereupon became redder than that over the rest of the body and so remained. At 5 months a reddened, apparently nontender lump was noted at the tip of the left second finger. This was believed to be a splinter and was treated with hot packs. At 6 or 7 months a small mass was noted in the left axilla. At 7 months raised areas suddenly appeared on the left forearm and on the dorsum of the left hand and continued to enlarge very slowly. At 18 months of age a particle of calcareous deposit was removed from the left second finger. This deposit subsequently recurred. At 2 years and 9 months another particle was spontaneously extruded from the distal end of the left middle finger. At 3 years, 5 months a small lump was noted in the scalp at the crown of the head.

When 3½ years old the baby was brought to the Children's Orthopedic Hospital. Routine blood studies showed normal hemoglobin, white count, and differential. The Mantoux was negative in 1 to 10,000 dilution and the Kahn was negative. Urinalyses were consistently normal. The urinary calcium excretion for twenty-four hours was 0.21 Gm. Serum calcium ranged from 8.1 to 11.8 mg. per cent. Serum inorganic phosphorus varied from 3.4 to 3.6 mg. per cent. The alkaline phosphatase was 3.8 Bodansky units.

Radiographs submitted with the patient showed apparent calcification in the soft tissues of the left axilla, arm, forearm, hand, and fingers. Recheck films in the hospital (Figs. 1, 2) were similar, but, in addition, showed an irregular destructive process at the distal end of the ulna with some periosteal reaction. Films of the right arm, skull, spine, pelvis, and legs showed no abnormalities.

From the Children's Orthopedic Hospital and the Department of Pathology of the School of Medicine of the University of Washington.
Presented before the North Pacific Pediatric Society, Spokane, Wash., March 20, 1948.

At this time two rather extensive explorations and dissections of several presumably calcified areas were done. Masses were removed from the left hand and forearm, upper arm, axillary fold, and chest wall. Some masses were intrautaneous, while others were in the subcutaneous tissue freely movable beneath the overlying skin. Some of these pieces were firmly attached to the underlying bony structure. Some were within the muscle or muscle sheath. These masses were white and varied markedly in size and thickness. (Fig. 3.) The edges were very irregular. No abnormality of the blood supply was noted. The distal joint of the middle finger was immobile with stony-hard, subcutaneous

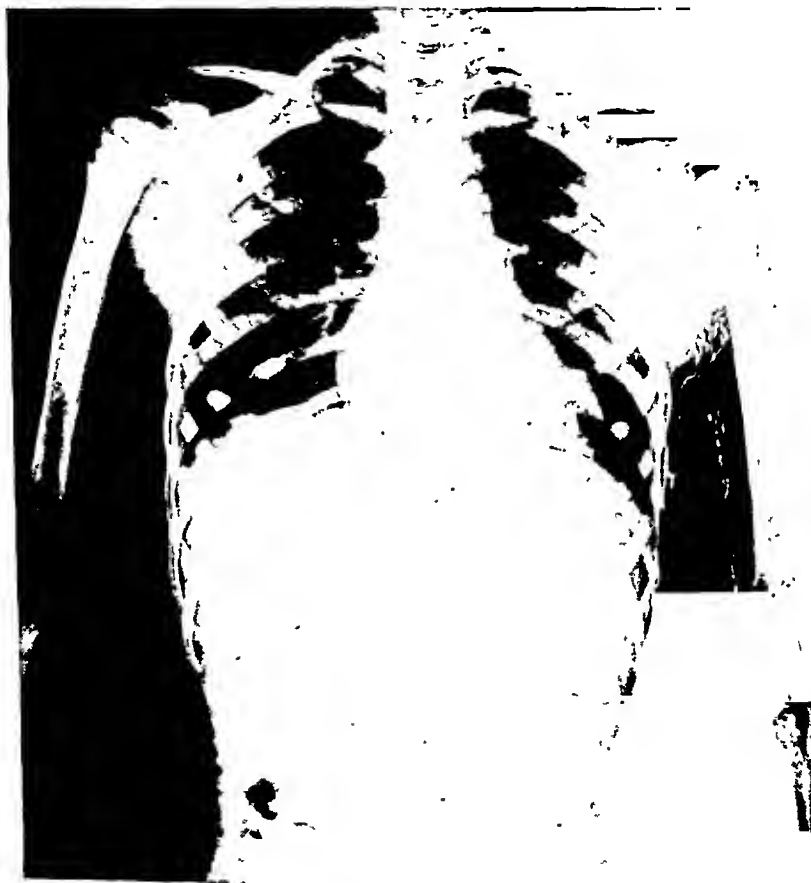


Fig. 1.—Radiograph showing heterotopic bone formation in muscle and muscle sheath, left axilla and arm.

masses firmly attached to the skin and bone at the site of previous, partial excision. The largest single piece lay on the dorsum of the left hand. It measured 1.5 by 3.5 by 0.4 cm. There was loose areolar tissue between this mass and a similar bony mass beneath it which was attached to the metacarpals. A mass in the left anterior axillary fold was attached to the undersurface of the skin and measured 1 by 2 by 0.2 cm. This piece was quite irregular with rough edges. An associated underlying mass lay within the sheath of the pectoralis muscle at its insertion, 1.5 cm. in diameter in the widest portion, tapering toward the anterior end and splitting rather widely toward the humerus.

Following these operations, the incisions healed without incident and without recurrence of the lesions. A full-thickness graft of skin grew satisfactorily upon the dorsum of the hand. The child remained in excellent health.



Fig. 2—Radiograph showing heterotopic bone formation in muscle, subcutaneous tissue and skin, left forearm, hand, and fingers

Microscopic examination of the surgical specimens showed not mere amorphous calcification, as was expected, but actual mature bone situated within the dermis and subcutaneous tissue (Fig. 4), within fascia and within muscle (Fig. 5). This bone possessed recognizable Haversian systems and centrally placed islands of well-formed red and fatty marrow. There were no inclusions

of cartilage and but small areas of osteoid at the periphery of the plaques where there were narrow mantles of fibrous tissue. The picture was such as to suggest at once congenital or developmental origin of the aberrant bone. There were no evidences of inflammation or of neoplasm.

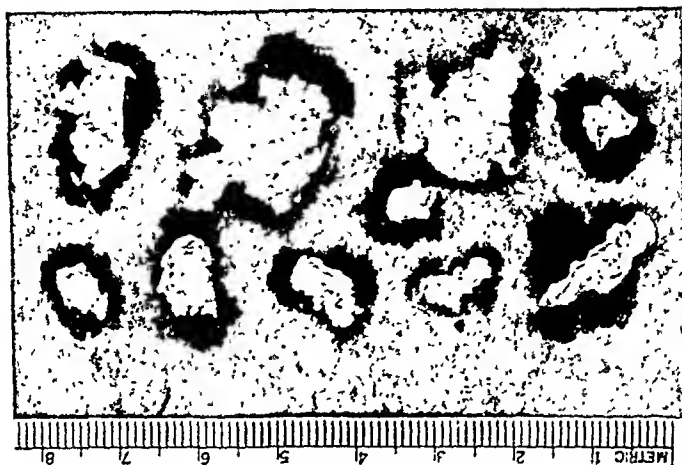


Fig. 3.—Portions of heterotopic bone removed from muscle and subcutaneous tissue, left upper extremity.



Fig. 4.—Microphotograph $\times 40$, heterotopic bone in dermis and subcutaneous tissue from dorsum of left hand. Note fatty marrow between trabeculae of bone. (Epidermis at top of figure).

A search of the literature has yielded only three other studies dealing with children.

1. Sherwell¹ and Coleman² of New York City reported a 6-year-old girl with plaques in the skin and subcutaneous tissue of the left fourth toe and the sole of the left foot.

2. Taylor and MacKenna³ of Liverpool, England, reported a 15-month-old girl with "gristly plaques" in the deeper layers of the skin distributed on the medial aspect of the right leg, on the outer side of the left thigh, on the left forearm, on the anterior and posterior aspects of the chest, and on the scalp.

3. Vero, Machacek and Bartlett⁴ of New York City reported a 3-year-old boy with "lumpy" plaques in the skin of the left side of the scrotum, the left thigh, left leg, left foot, left buttock, and the back. The scrotal lesions were noted at birth, and the others developed in groups, from the age of a few weeks to 2 years. As in our case, there was spontaneous extrusion of small concretions, mainly on the toes, which first became reddened, swollen, and tender; there were also deeper seated intramuscular masses of bone developed within the left buttock and in the left popliteal region.



Fig. 5.—Microphotograph $\times 40$, heterotopic bone in left pectoral muscle. Note hemopoietic marrow between trabeculae of bone. (Remnant of muscle in lower right-hand corner of figure.)

In these three cases, as in ours, biopsy of the plaques demonstrated not mere calcification, but mature bone with marrow situated within the deeper layers of the dermis. The lesions were multiple in all cases, though varying considerably in number and extent. Though the follow-ups in these cases were rather limited, there seems to be agreement that the lesions did not recur when removed. In one of the cases new lesions appeared at other sites following removal of some of the plaques. In none of the cases was there a history of antecedent trauma, inflammatory process, or other possible inciting agents. The condition was designated "osteosis of the skin" by the first authors, "osteoma cutis" by the second group of authors and "congenital osteomas of the skin" by the third group.

It is our feeling that the development of plaques of mature bone within the deeper layers of the dermis, within the subcutaneous tissue, and within muscle is a localized tissue malformation, properly designated as a heterotopia—a formation of normal tissue at an abnormal site. The segmental distribution

of the lesions, apparent both in our case and in the case of Vero, Machacek, and Bartlett,⁴ is reminiscent of that occurring in some other structural developmental abnormalities such as fibrous dysplasia of bone of Albright and collaborators⁵ and of Lichtenstein and Jaffe.⁶

The condition under consideration is to be differentiated from the types of calcinosis, processes in which amorphous calcium is deposited in tissue. Localized calcinosis usually occurs in adults. Disseminated calcinosis occurs more often within the first two decades of life. It is sometimes associated with scleroderma, or with Raynaud's disease or other type of vasomotor abnormality. Both the localized and disseminated forms are rare and of unknown origin.

In traumatic ossifying myositis, formation of actual bone may follow deposition of calcium in muscle that has been subject to trauma. This is a hazard of football and other vigorous occupations of adolescence.

Progressive ossifying myositis is a rare disease with familial incidence, affecting male persons predominantly, extending into adult life. Plaques of bone are formed in continuity with the skeleton, and in addition plates of bone appear within fascial planes between the muscles. In three-fourths of the reported cases, the great toes are abnormally small, with ankylosis of the proximal interphalangeal joint.

In the several forms of calcinosis and of ossifying myositis there is, as in the heterotopic bone formation, no demonstrable alteration in calcium metabolism. Laboratory studies are, therefore, useless in differentiation of these diseases. In contradistinction are the cases of metastatic calcification occurring in primary hyperparathyroidism or in renal rickets, with elevation of the blood calcium, lowering of the blood phosphorus, and increased urinary excretion of calcium.

The prognosis in heterotopic bone formation is necessarily uncertain, as none of the few case reports includes a long follow-up period. Consideration of the nature of the tissue changes suggests nonrecurrence, though some new lesions may be expected to develop after removal of earlier ones.

It is proposed to excise the plaques remaining in our patient and such additional ones as may arise subsequently in the belief that there will be no recurrence.

SUMMARY

Heterotopic formation of mature bone within the deeper layers of dermis, subcutaneous tissue, and muscle appears to be a rare malformation of segmental distribution occurring in young children. Simple excision is employed in treatment with apparent curative results. To the three cases found in the literature a fourth has been added.

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PRENATAL AURICULAR FLUTTER

HAROLD E. STADLER, M.D.

INDIANAPOLIS, IND.

AURICULAR flutter is rarely noted in juvenile heart disease and actual prenatal arrhythmia with later demonstration of true auricular flutter has rarely been reported. Carr and McClure¹ noted fetal cardiac irregularity during the last month of gestation. Electrocardiographic proof of auricular flutter was given about twenty-six hours after the birth of the infant. Rhythm and rate returned to normal on the tenth neonatal day.

Sherman and Schless² reported upon findings in a 3-month-old male infant with occasional cyanosis and syncope. During the eighth gestational month, the rate was too rapid to count, although on one occasion a rate of 190 beats per minute was found. Electrocardiographic verification led to treatment with tincture of digitalis and restoration of normal rate and rhythm. The authors concluded that maturity of the conduction bundle established the normal mechanism.

D. Me. was born on July 24, 1947, by classical cesarean section. Dr. Ross E. Griffith furnished the following obstetrical record:

<i>Date</i>	<i>Fetal Heart</i>
May 2, 1947	Rate, 156 beats per minute
June 6, 1947	Irregular
June 30, 1947	Rate, 208 beats per minute
July 5, 1947	Very rapid and irregular
July 12, 1947	Irregular: rate, 180 per minute
July 21, 1947	Irregular: rate, 136 per minute

The mother of the patient, a 41-year-old gravida v, para v, began to have profuse vaginal bleeding on the morning of July 24, 1947. An x-ray of the abdomen led to the finding of placenta previa. The health of the patient had been excellent during her entire pregnancy.

The infant was 51 cm. long and weighed 7 pounds, 13 ounces. Examination was entirely negative except for moderate cardiac enlargement and cardiac rate of 240. There was an inconstant, faint, systolic, precordial murmur. Transitory arrhythmia and cardiac rate of 150 to 160 beats per minute were noted. The infant was apathetic and nursed poorly. At no time was there evidence of congestive failure until on July 28 when definite sclerema was noted involving both thighs, particularly on the lateral aspect. Sclerema neonatorum has been held to be indicative of impaired circulation.

An attempt was made to stop the arrhythmia through vagal pressure but this proved unsuccessful. On August 4, quinidine sulfate was given in dosage of $\frac{1}{4}$ grain every four hours. The heart rate dropped to 112 to 120 per minute but the baby began to vomit feedings and to lose weight. The quinidine was stopped and within eighteen hours the heart rate was again over 200 beats per minute.

From the Departments of Obstetrics and Pediatrics, the Methodist Hospital, Indianapolis.

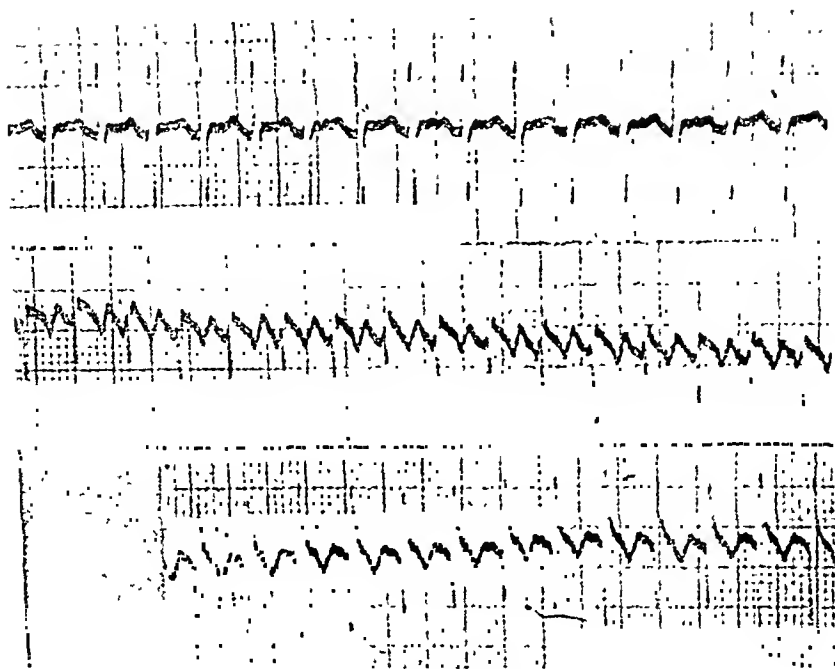


Fig. 1.—Electrocardiogram taken on July 30, 1947, showing auricular flutter with 2:1 conduction ratio in the limb leads.

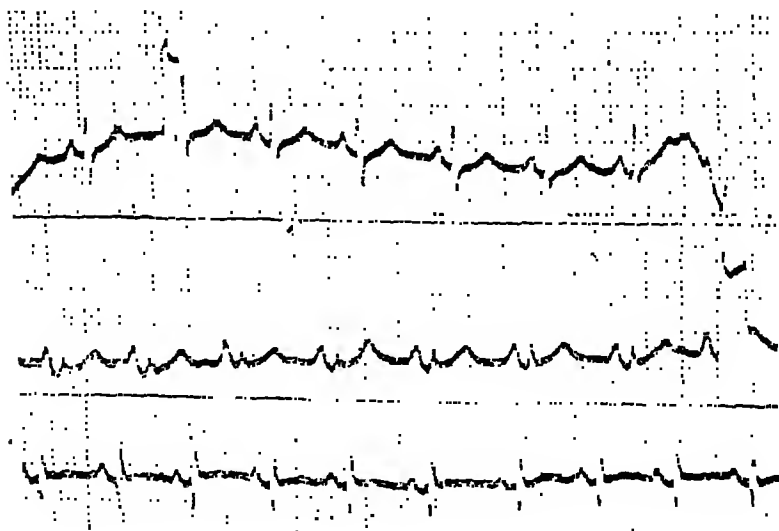


Fig. 2.—Electrocardiogram taken on Nov. 26, 1947, showing a sinus rhythm.

On August 15, Crystodigin (Eli Lilly Company) was given. An ampule of this preparation (1 c.c. containing 0.2 mg.) was diluted to 20 c.c. with sterile water and one teaspoonful (0.04 mg.) was given every six hours. Within thirty-six hours after the medication was begun the rhythm was normal and the heart rate was 120 to 128 beats per minute. The Crystodigin was given for three full days and then stopped. The weight of the infant began to increase normally. At the time he was $3\frac{1}{2}$ months old, the baby weighed 16 pounds. The murmur could no longer be heard and cardiac size was normal. The infant weighed $23\frac{1}{2}$ pounds and was $30\frac{1}{2}$ inches long when he was 9 months old. Physical examination was entirely normal. There was no evidence of heart disease. The sclerema had disappeared.

SUMMARY

A case of prenatal auricular flutter (apparently the third reported) is presented. Therapy with quinidine sulfate proved effective but toxicity led to its withdrawal. Crystodigin therapy established a cure. It has been stated that the large diphasic QRS complexes in the first curve and tall P waves in the second curve are suggestive of congenital heart disease. Observation of the patient will continue although all factors involved point to the fact that a complete state of normality has been established.

The author expresses his appreciation to Drs. I. H. Zitman, Chicago, Ill., and E. Blatt, Indianapolis, Ind., for their electrocardiographic interpretations and to Dr. Ross E. Griffith, Indianapolis, Ind., for use of his records and for his deep interest in this study.

The Eli Lilly and Company, Indianapolis, Ind., furnished the Crystodigin.

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EMBRYONAL ADENOCARCINOMA OF THE TESTICLE IN A THREE-YEAR-OLD CHILD: REPORT OF A CASE

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CHICAGO, ILL.

CARCINOMA of the testicle in childhood is a rare condition, but a review of the literature indicates a frequency sufficient to make one suspect the diagnosis when a rapidly growing, firm, nontransilluminable mass is discovered in the scrotum of an infant or child.

Dean¹ reported a series of 500 cases of testicular teratomas in all ages. Eight of these occurred in children up to the age of 14 years, an incidence of 1.6 per cent. Paget² noted that tumors of the testis constitute 2.8 per cent of all tumors in infants.

Julien,³ in a treatise on tumors of the testis in children, collected 137 cases. He noted that the incidence is highest during the first three years of life, and declines toward puberty. Kutzmann and others,⁴ in a review of the literature, quote Steffen and Gerhardt who found that tumors of the testis occur chiefly in infancy, gradually diminishing in frequency in the second, third, and fourth years.

Practically all testicular tumors in infants are mixed or teratomas, and the so-called seminoma is exceedingly rare. Chevassu⁵ noted that five of 61 cases of teratomata occurred in children, whereas in a group of 59 such tumors there were no cases of seminoma in children. Dean¹ stated that, histologically, tumors of the testis in children are similar to those in adults. The bulk of these tumors consists of highly anaplastic embryonal cells. Adult structures with much greater cellular differentiation are also present.

CASE REPORT

A 3-year-old white male was admitted to Sarah Morris Hospital on July 30, 1947, with acute respiratory distress, characterized by wheezing, obstructed breathing, and elevated temperature. Physical examination and roentgenograms confirmed the diagnosis of bronchopneumonia. The respiratory symptoms responded promptly to medical management.

It had never been noted prior to admission that there were any genital abnormalities. It was discovered in the course of the admission physical examination that the right testicle was four times larger than the left. It was insensitive, nodular, firm, and did not transilluminate. The right epididymis and vas deferens were normal. There was no lymph gland enlargement. The left testicle was normal.

A clinical diagnosis of tumor of the right testis was made, and urologic consultation was requested. The patient was seen by Dr. Irving J. Shapiro, who concurred in the diagnosis and advised orchidectomy.

On Aug. 5, 1947, a right orchidectomy was performed. The postoperative course was uneventful. The dressings were changed and the sutures removed on the fourth postoperative day. The wound healed by primary intention. The patient was discharged on Aug. 9, 1947, and returned to his home in another state where intensive radiation therapy was given.

From the Sarah Morris Hospital, and the department of urology, Michael Reese Hospital, pediatric service of Dr. Philip Rosenblum.

Pathologic Report.—The specimen consisted of a testicle including the epididymis. The entire specimen measured $2 \times 2 \times 1.5$ cm. The tunica vaginalis as well as the mesothelial covering of the epididymis and portion of the vas were smooth, gray, and glistening. The testis was deformed. On section, it was occupied almost entirely by a soft tumor which presented a pleomorphic appearance. Some portions were red, others bright yellow. The latter appeared as islands which were somewhat more elevated than the surrounding zones. The tumor occupied the entire testis except for a thin rim at the upper pole. Tumor could not be noted in the epididymis, tunica vaginalis, or any other surrounding tissue. The epididymis and vas revealed no gross changes.

Fig 1

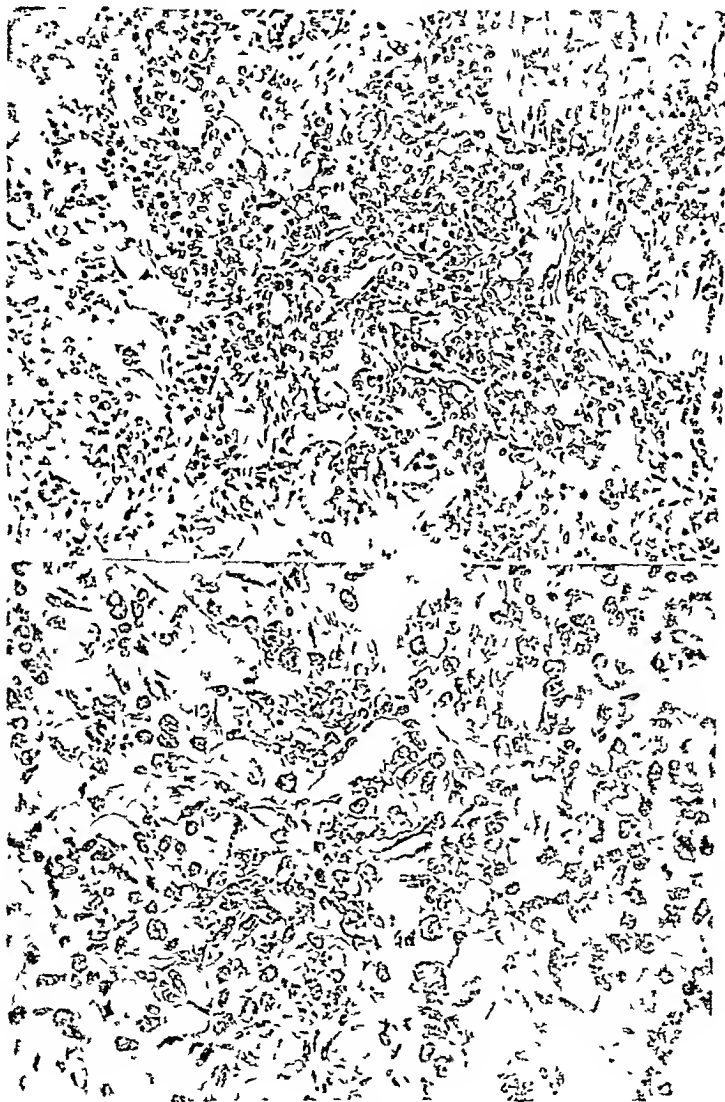


Fig 2

Fig 1—Photomicrograph of testicular tumor, low power

Fig. 2—Testicular tumor, high power

Microscopic appearance is represented in Figs. 1 and 2. The sections consist of tumor cells arranged in masses or pseudoglandular formations, lying in a loose stroma. The cells are large and differ markedly in size and shape. The nuclei present a dense nuclear membrane but relatively scant chromatin material, and one or two prominent nucleoli. There are numerous typical and atypical mitotic figures. The cytoplasm is copious and clear or vacuolated. The stroma consists of loosely arranged fibroblasts and numerous dilated capillaries.

Pathologic Diagnosis: Embryonal adenocarcinoma of the testis.

SUMMARY

A case of carcinoma of the testis in a 3-year-old child is presented together with a brief review of the literature as to incidence and types of carcinoma of the testis in children.

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Erratum

In the article entitled "Generalized Vaccinia" on page 281 of the September, 1948, issue of THE JOURNAL, the name of the second author, Dr. Philip Hedrick, has been misspelled.

Clinical Conference

CONFERENCE AT THE ST. LOUIS CHILDREN'S HOSPITAL

JULY 30, 1948

ALEXIS F. HARTMANN, M.D., CHIEF-OF-STAFF

Case 1. Ovarian Tumor

DR. (GERALD HUGHES.—The first case this morning is that of M. R., a 7-month-old white girl who was admitted to the St. Louis City Hospital on July 17, 1948, with the following history (which, as it turned out, proved more confusing than helpful):

The infant had been in good health until May 14, 1948, when, following the ingestion of some applesauce, she developed cramping abdominal pain, some fever, and passed several loose stools, one of which was blood-streaked. She was seen by a local physician, who advised the parents that the infant had an ear infection and gave her an injection of penicillin.

The next morning she seemed perfectly well again and remained so until July 15, 1948, when, following the ingestion of pears from a freshly opened can, she again developed cramping abdominal pain. She was very irritable and vomited once that evening and again the following morning. Later that morning she developed a fever and during the day had five bowel movements.

She was seen in the Receiving Room of the St. Louis City Hospital on the evening of July 16. At that time physical examination was nonrevealing except for some fever and irritability. The parents were told to omit all feedings for twelve hours and to bring the infant back the following day if she showed no improvement.

Feedings were resumed on the morning of July 17, and all were retained. The infant had one normal bowel movement that morning. However, the complaints of fever, irritability, and cramping abdominal pain persisted, and, in addition, the parents noted that her abdomen seemed more full than usual. She was brought back to the hospital on the afternoon of July 17.

At that time physical examination revealed a pale but well-developed and well-nourished infant who was quite irritable and appeared acutely ill. The abdomen was distended and there was generalized tenderness and voluntary muscle guard. No organs or masses were palpated at that time. Bowel sounds were hypoactive. Rectal examination revealed no tenderness or masses. The remainder of the physical examination was not abnormal except for the left tympanic membrane, which was thick and dull.

The infant was admitted to the hospital with the diagnosis of possible acute appendicitis.

Laboratory examination revealed the urine to be normal. The hemoglobin was 7.1 Gm. The white blood cell count was 18,800, with a marked left shift. Blood Kahn was negative.

A diagnostic abdominal paracentesis was performed in the right flank. A few drops of thin, bloody fluid were obtained, but it was felt that this fluid had not been obtained from the abdominal cavity. Smear of this fluid revealed no organisms, and a culture reported later revealed no growth.

The infant was given a transfusion of whole blood and started on penicillin, streptomycin, and sulfadiazine subcutaneously. A small enema was given with the return of soft, yellow stool. Wangensteen suction was begun.

The following morning, July 18, the infant's abdomen seemed less distended and was soft to palpation when she was quiet. No organs or masses were palpated.

On the morning of July 19 vaginal bleeding occurred, and drew our attention again to the presence of mild hypertrophy of the breasts and an excess of pubic hair, both of which had been observed but not considered significant. Vaginal examination revealed rugae increased in number and hypertrophied with bloody fluid seen coming through the cervix.

That afternoon, under anesthesia, a mass was easily felt in the right lower quadrant. Upon opening the abdomen a mass approximately 12×15 cm. in size was found lying in the right lower quadrant of the abdomen but attached to a pedicle extending to the left lower quadrant. It was hemorrhagic and necrotic and was attached to the left Fallopian tube, which also was greatly distended and hemorrhagic. The mass was twisted three times on its pedicle. The right ovary and adnexa and the uterus all seemed to be normal.

Histologic examination of the mass removed has so far been unsatisfactory because of the amount of autolysis which took place. A diagnosis of cystic tumor of the left ovary with hemorrhage and necrosis was made.

Postoperative course was uneventful except for a transitory elevation of temperature on the second postoperative day and the passage of one tarry stool on the third postoperative day. The infant was discharged from the hospital on the eleventh postoperative day.

DR. DON THURSTON.—This infant presented a somewhat difficult problem during the first forty-eight hours of hospitalization in that not only was the examination difficult, but its results were unsatisfactory. At the time of admission, with the evidence of impending shock and a blood picture suggesting the loss of blood and the presence of acute infection, we had difficulty in explaining all of the symptoms and signs on the basis of a single disease. The possibility that we were dealing with a surgical abdomen was uppermost in our minds. The patient's condition seemed too critical to tolerate an exploratory surgical procedure, and we felt that all we could do was to administer parenteral fluids and blood. The history of the onset of symptoms shortly after the ingestion of food suggested the possibility of food poisoning due either to preformed toxins or to bacterial invasion. The symptoms of severe food poisoning are usually dramatic and are characterized by severe nausea, vomiting, abdominal pain, acute prostration, and diarrhea, with profuse sweating, hypotension, and shock, and, in the case of botulism, there is the curare-like action of the poison on the motor nerves and voluntary muscles. This child, however, had very little diarrhea or vomiting and no evidence of neurological changes.

With the persistence of the picture and with no evidence of infection elsewhere, it was felt advisable to attempt an abdominal paracentesis. This type of aspiration is done carefully with a small needle. The abdominal cavity is entered laterally with the bevel up, and mild suction is applied. Any material obtained is smeared on a sterile slide and stained. The remainder is cultured. By this means it is possible to differentiate primary from secondary peritonitis. The symptoms and physical findings in this infant were compatible with either diagnosis.

Other surgical conditions considered were: congenital anomalies with partial obstruction, intussusception, mesenteric lymphadenitis, and urinary tract infection, all of which conditions seemed to be ruled out on the basis of history and physical findings and the course while under observation.

At this point a review of the history again revealed a small point—that of recurrent but persisting breast enlargement. A direct examination of the genitalia revealed a definite but slight increase in the size of the labia and the presence of hair which was definitely unusual for this age group. On the third hospital day the infant had vaginal bleeding, sudden in onset and moderate in amount, of a serosanguinous nature. A smear of this material revealed no leucocytes but large polygonal cells with some evidence of nuclear degeneration. Vaginal examination with a speculum proved that the blood was coming from the cervix. The vaginal mucosa was definitely thickened with increased folds. The feeling of the observers was that we were dealing with a menstrual type of bleeding. With the child's condition improved, an exploratory laparotomy was done. At the time of operation and with the infant under anesthesia, a definite globular mass was both visible and palpable in the right lower quadrant. The preoperative diagnosis of ovarian tumor seemed to be correct, and on opening the abdominal cavity the diagnosis was confirmed.

In reviewing the cases published, the unusual feature in this case is the onset of menstrual bleeding following the torsion of the pediculated tumor. In recent years the effect of estrogens on the female human being has been widely investigated, and it is interesting to note that in this case, even with evidence of precocity, there was no bleeding until torsion of the tumor interfered with the blood supply. After experimental therapy with estrogen has been stopped, it is usually five to seven days before menstrual bleeding takes place. This concurs. Also, the vaginal thickening, breast enlargement, and some increase in size of the labia are the normal effects of estrogen in the prepubertal, castrated female. The microscopic sections are difficult to evaluate as to the type of tumor, because of autolysis. There are, however, two types of tumors that give rise to this type of precocity, the granulosa cell and the thecoma or thecal cell tumor. The manifestations in both are due to excess estrogen formation, and differential diagnosis is made microscopically. From the cases reported the prognosis seems good, but recurrences have occurred.

DR. PETER HEINBECKER.—I wish to present a case we had a few months ago. The child, 1½ years of age, was admitted extremely ill. The chief positive findings were those referable to the general appearance and to the abdomen, which was greatly distended. It was felt that the distention was due to fluid.

within which a tumor probably was located. A needle was inserted and some chocolate-colored fluid obtained. The child had prominent breasts and pubic hair was present; the labia were somewhat enlarged; the clitoris was not enlarged. The child looked older than her age and the eyebrows and hair were thick.

At operation there was found a large, right-sided, ovarian cyst with the pedicle partly twisted. The pelvic structures on the left side were normal. The uterus was slightly enlarged.

On microscopic section a typical thecal cell tumor was diagnosed. There were many small spaces lined by secretory cells.

The child has not been seen since the time of discharge. It is expected that she will show a recession of the signs indicating an excess estrogen secretion.

DR. ALEXIS F. HARTMANN.—Dr. Thurston, is it not fair to state that as soon as more or less emergency treatment had been rendered this child (fluid administration and blood administration) the over-all picture then suggested a serious intra-abdominal condition that one would ordinarily associate with a surgical lesion sometimes found with appendicitis, especially with localized abscess formation, or a Meckel's diverticulum with peritonitis or abscess formation? Having reached the point where one had to consider the child as requiring surgical intervention regardless of what might be found, ought not the baby to have been explored without further delay? Do either of you, Dr. Veeder and Dr. Cooke, remember any child in whom a diagnosis was not made sufficiently early in the case of a twisted ovarian pedicle or any other ovarian cyst with hemorrhage into it? What should we expect to happen if a diagnosis is not made and proper surgery performed?

DR. HEINBECKER.—Under those circumstances invasion of the tumor by organisms may lead to peritonitis. An aseptic peritonitis only may occur.

DR. HARTMANN:—The picture of a pelvic abscess?

DR. HEINBECKER.—Diffuse pelvic and abdominal peritonitis.

I should have mentioned that in this case withdrawal bleeding also occurred on the third day following removal of the tumor. The bleeding from the uterus lasted for three or four days.

DR. HARTMANN.—Dr. Thurston, would you regard this vaginal bleeding as similar to the bleeding seen in newborn babies as the result of deprivation of estrogen?

DR. THURSTON.—Yes, quite similar in character. This child had menstrual bleeding on the sixth day.

DR. HARTMANN.—However, the breast enlargement seems to be different from that in newborn babies. The breasts are not engorged but are definitely enlarged. There is protrusion, not retraction, of the nipples.

If you had not found the tumor, would you have been much impressed by the pubic hair or breast enlargement in this baby?

DR. THURSTON.—Yes, I was impressed with the pubic hair and pointed it out on several occasions. It seemed too much for this age. It was quite sug-

gestive of a patient of Dr. Hartmann's and suggestive also of a patient with endocrine dysfunction—the dwarf—in which definite increase in pubic hair was seen. There also seemed to be some pigmentation of the skin which was not due to sunshine, because it has faded a little too fast.

DR. HARTMANN.—Do you think you should have been able to feel this mass rectally?

DR. THURSTON.—Under anesthesia, yes, but not without anesthesia. Numerous rectal examinations were made, but no mass could be felt.

DR. PARK J. WHITE.—There is much in this case to attract attention to the genital system. Did you find any trouble with the appendix? I have cited previously a patient with an acute appendix in addition to an ovarian cyst of this type. Which came first? The acute appendix or the ovarian cyst? Undoubtedly, the ovarian cyst came first, but the appendix was inflamed as well.

DR. READ BOLES.—The appendix in this case was not explored.

Cases 2 and 3. Esophageal Stenosis Following Ingestion of Lye

Case 2

DR. RALPH LUCE.—This patient, H. B., is a 2-year-old Negro girl who entered Children's Hospital seven weeks ago. She had been well until one week before entry when she drank a glass of milk containing two tablespoonfuls of lye. She suffered severe burns of the mouth and was taken to another hospital for four days where she received penicillin and parenteral fluids. She was able to swallow only fluids during the three days prior to entry to this hospital.

With a barium swallow a constriction was seen in the esophagus about one or two inches above the stomach. Attempts to pass a weighted string into the stomach were unsuccessful. An esophagoseopy was then done, which revealed a slitlike stricture 22 cm. from the central incisors. Gradually less food could be taken orally, and parenteral feedings were necessary during the third week in the hospital.

Three weeks after entry and four weeks after the original injury the esophageal stricture with the segment of esophagus distal to it was excised and an esophagogastrostomy and vagotomy were performed. The immediate postoperative course was uneventful. When oral feedings were resumed, the patient took them without difficulty in swallowing and without vomiting. Eighteen days after the operation she began to refuse much of her feedings. This seemed to be corrected when a more palatable diet was offered; however, the past four days she has again refused a large part of her food. She has regurgitated a small amount twice during this time.

A barium swallow done six days ago revealed a functioning esophagogastrostomy.

This x-ray (Fig. 1) of the barium swallow taken prior to operation demonstrates a constriction of the lumen in the distal 3 to 4 cm. of the esophagus with a dilatation of the esophagus superior to the stricture. The barium mixture is seen to pass through the stricture in a trickle.

The barium swallow done last week (Fig. 2) shows prompt deglutition, barium passing promptly through the artificial stoma into the stomach. There is eventration of the diaphragm, so that the stomach is displaced upward.



Fig. 1.

DR. ALEXIS HARTMANN.—I think this is our first child to be operated on with the bringing up of the stomach into the thorax and anastomosis to the esophagus. It is of interest to consider that we have essentially created a condition which we sometimes think is necessary to correct surgically—a diaphragmatic hernia with the stomach in the thorax. We recall, too, that in the last year or so Dr. Fields reported on four very interesting children, each born with a congenitally short esophagus, who later began to regurgitate food, often mixed with blood. Are we going to have trouble of that sort with this operation, which otherwise seems almost perfect? You remember that the piece of esophagus resected and shown to us a week or two ago was very fibrous. Everyone agreed that it could never have been dilated successfully. Because a piece of the vagus nerve was resected in this child, the danger of such peptic ulceration is probably considerably minimized. The results in treatment of peptic ulcers suggest that such vagotomy is of considerable value.

DR. ROBERT SCOTT.—What period of time was there between the swallowing of the lye and the operation?

DR. LUCE.—Four weeks.

DR. SCOTT.—Is it possible that that operation was performed a little soon after ingestion of the lye and that stricture might have developed higher up after operation?

DR. PAUL J. ZENTAY.—That is not likely after four weeks. It has been demonstrated by x-ray that there is no other stricture.



FIG. 2.

DR. HARTMANN.—There is nothing to indicate stricture in the upper portion, and it is amazing to see how much scar formed in the lower segment in the four weeks following the injury. If some constriction should still develop in the upper portion, it ought not to be difficult to dilate from above.

DR. SCOTT.—A word about vagotomy. I saw some adults in San Diego who had this done for recurrent peptic ulcers, and they developed symptoms of diarrhea, etc. following vagotomy. It is not an entirely benign procedure.

DR. HARTMANN.—In one of our infants born with esophageal atresia, following esophageal anastomosis the vagotomy syndrome made its appearance and resulted in marked gastric atony and much regurgitation which finally led to dehydration and alkalosis. In that child Urecholine seemed to be of value in stimulating gastric peristalsis. Eventually this child recovered.

DR. ZENTAY.—How much vagus nerve was resected?

DR. HARTMANN.—About 4 cm.

Case 3

DR. C. W. DAESCHNER.—D. E., a 34-month-old white boy, was first admitted to Children's Hospital on July 30, 1947, at the age of 21 months because of inability to swallow. The mother stated that in September, 1946 (twenty-two months ago), the patient swallowed some lye solution, resulting in burns of the mouth and esophagus. He was hospitalized for three days and given penicillin. No other therapy was given. After healing, the patient was able to swallow only strained foods and liquids, so he was hospitalized again and the physician said that there was pressure on the esophagus but that it was too low to stretch the esophagus. The patient was transfused and dismissed. In the interim he has remained on a liquid diet, gained weight, and done well until three days prior to the original admission to Children's Hospital, when he developed a cough and with it inability to retain any solid food and only very small portions of water. Food would be swallowed and then regurgitated immediately.

On admission, the patient was thin, pale, dehydrated, and febrile (39° C.) with mild acidosis and acute pharyngitis. As soon as the physical condition improved, a dilatation of the esophagus was done under anesthesia. A stricture was visualized 13 cm. from the incisor teeth. Bongie dilators were inserted up to No. 16. Following this procedure, the patient's ability to swallow was much improved and milk and water were then taken comparatively well. Dilatation was repeated three days later to a No. 20 bougie which passed with some difficulty. After this therapy, subcutaneous fluids could be omitted, and the boy could handle a regular infant diet quite well. Dilatation was repeated four days later, this time to a No. 20, and progress was so good that it was decided that dilatation could be carried out only once weekly. He was dilated for the fourth time one week later. At this time a No. 4 bronchoscope was passed through the first stricture down to the second series of strictures and through these. The patient was then discharged on a regular diet to return in two weeks.

Two weeks later the patient was readmitted in good condition and was able to swallow a regular infant diet (milk, Pablum, orange juice, water, etc.). This time a No. 4 bronchoscope and a No. 9 bougie were passed through both strictures. Results were good, and the patient was dismissed to return in three weeks for dilatation.

At the time of readmission three weeks later, the child was still on a regular diet, now including cereals, crushed spaghetti, strained vegetables, and all liquids. The patient was dilated as before and dismissed in good condition.

He was readmitted (this time to McMillan Hospital) three weeks later and dilated as before with good results and told to return in one month.

He was readmitted in December and this time dilated to a 5 mm. bronchoscope, and the second stricture was described as spiral in type. He was discharged improved.



Fig. 3.

Five months later he returned to Children's Hospital with the story that he could not even swallow his own saliva for the past two days, but after hospitalization ability to take fluids orally returned spontaneously. When the patient was hydrated, esophagoscopy was done with a No. 6 scope passed to a pinpoint stricture 16 cm. below the incisors, and bougies up to No. 16, were passed through the stricture down to a 50 cm. level. Repeated attempts were then made to allow passage of a shot on a string, but each time the shot lodged at the stricture.

On June 29, 1948, the patient was esophagoscoped, a 35 Jackson scope being passed without difficulty through the stricture at 14 cm. below the upper incisors. The stricture was described as firm, annular, with a 3 to 4 mm. lumen, and the mucous membrane for 1½ cm above the stricture was pale and scarred.

Several radiographic studies of this patient have been made over the period of his stay at Children's Hospital. These are all similar, so that the most recent anteroposterior and lateral views (Figs. 3 and 4) taken with a thick barium swallow serve to illustrate the esophageal deformities. The first stricture, which represents the one described as 14 cm. from the incisors, is visualized just below the dilated portion of the esophagus and just above the manubrium. It is about $\frac{1}{2}$ cm. in diameter. The second stricture is visualized approximately 2 cm. lower and, in the lateral view, is seen to be 4 to 6 cm. long and with a 2 to 3 mm. lumen. No other evidence of stricture or anomaly of the esophagus is noted.



Fig. 4.

DR. HARTMANN.—This is a problem because the stricture begins high, is multiple, and involves the larger portion of the esophagus. It would seem fairly obvious that the relatively simple operation which had been performed in the girl, bringing the stomach up and anastomosing to the good upper part of the esophagus, would not work well here because too little good upper esophagus is left, and also it would seem that the operation described to us a few weeks ago by Drs. Burford and Bricker, of making a new upper esophagus by

means of a skin tube, would in itself not suffice. It would solve the difficulty of the upper esophagus but not the lower esophagus. So this child would have to have both operations, the tube for the upper and the anastomosis for the lower portion. This child, while in excellent condition, is getting worse. He has lost several pounds in the last few weeks and takes longer to eat. Many unsuccessful attempts have been made to dilate from above. Now the question is: shall we go ahead and do with him what we have usually done? Shall we do gastrostomy and then make further attempts to pass a string, so that dilatation with bougies would be possible? Recently it has been emphasized that once you do gastrostomy, you immobilize the stomach and prevent bringing it up any distance into the chest for anastomotic procedures. That knowledge has made us hold off until now. Are we correct in concluding that our experiences and results with gastrostomy and retrograde dilatation in the past, have been so poor that we should discard that procedure? Some think so, and some do not. Dr. Webb has gone over all of our cases and will give you a picture of what has happened. It is my hope that Dr. Webb's analysis will make it easy for us to say whether we should go back to our old method with this child.

DR. BAILEY WEBB.—You have just heard presented the cases of two children who swallowed lye. They are both about 2 years of age and were taken to hospitals as soon as the accidents were discovered. Early treatment was conservative, and the children were not seen here until after strictures had formed. The first child had a low stricture and was treated surgically. The problem of the management of this second child with multiple strictures prompted us to review the records of our previous cases and their outcome.

Since 1926, there have been thirty-eight patients with lye burn of the mouth and esophagus admitted to St. Louis Children's Hospital, twenty-nine white and nine Negro children. Although the ages varied from 5½ months to 7 years, the majority of these patients were between 1 and 3 years of age. Nine of the children were seen here less than forty-eight hours after the accident, and twenty-nine had some evidence of stricture at the time of entry. The incidence of strictures was higher after the ingestion of dissolved lye, but nine cases of stricture developed from taking powdered lye.

In all patients there was an initial anorexia, and many were never able to take solids well. The usual story is that after the mouth heals, swallowing improves, but this is followed by increasing dysphagia, first for solids and then for liquids. In most cases it becomes a serious problem in from 2 to 4 weeks, but in one case the time was less than one week and in three cases, more than two months. There were slightly more burns in the upper third of the esophagus than the middle and lower thirds.

In ruling out the diagnosis of stricture, unless thick barium is used the barium swallow may be misleading. On my initial examination of the first child presented today, I failed to see a stricture when using thin barium, and examination of the records shows that to have been the experience of the pediatrician and roentgenologist on occasion.

The treatment of these patients depends on whether or not they are seen before or after the stricture has formed. It is pathetic to note that at least thirty of the patients in our series were seen by a physician within forty-eight hours of the ingestion of the lye and that most of the parents were instructed to give the child some local mouth care and told that all would be well. Several of the parents reported that the children spat out the lye and that the doctor felt that only the mouth was burned at the time.

Of the nine children seen at the St. Louis Children's Hospital early, only two developed strictures. One was the first patient, in 1926, and the other a recent 5-year-old boy who drank a very caustic boiler compound.

The routine early treatment consists of frequent sips of orange juice for the first forty-eight hours. Beginning at the end of this time, mercury-filled bougies are passed daily, starting with the 14 French and rapidly increasing the size and length of time of dilatation until on the fourth day a 30 French bougie is left in place for thirty minutes. Dilatation with the 30 French is thus continued daily for at least two weeks, every other day for two weeks, twice a week for two months, once a week for two months, every other week for two months, and monthly for five months. Strangely enough, if the procedure is done with firmness and sympathy, it is tolerated well. Blind dilatation from above is stopped if evidence of stricture occurs, and other methods of treatment are used.

After strictures have formed, the patients usually have been treated by dilatation from above under direct vision or by gastrostomy with retrograde dilatation. There have been seven patients treated by the first method, one the patient under discussion. Three of these have been seen one to ten years after the treatment with some complaint of dysphagia; three have not been heard from, and one died in 1934 from perforation of the esophagus by an esophagoscope. Twenty patients have been treated by the method of retrograde dilatation. Eight of the patients have been followed until the gastrostomies were closed, and although there was a latent period between the last dilatation and the closure of the gastrostomy, none reported any dysphagia at the time of the closure, and there is a follow-up on only one, who reports occasional difficulty with the swallowing of solids. Seven are still being followed in ENT Clinic and have their gastrostomies still open. One child died of measles and pneumonia, and we have no information at present on four others. Though the gastrostomies were usually closed in from one to three years, one child has had one for five years. The thing that impressed me most was the technical difficulty the ENT man encountered in passing the string if the stricture were very small. Usually three weeks or more were required for this after gastrostomy, and in one case it took three years.

Two patients have been treated surgically, the child presented today and one child for whom Dr. J. B. Brown constructed an external skin-lined tube in 1938. This child was operated on two years after his stricture had become complete. Dr. Brown has no follow-up on this boy.

As stated above, we have had only two deaths, one from mediastinitis before the days of chemotherapy and one from an intercurrent infection.

Considering the numerous esophagoscopies, it is a tribute to the ENT staff that there have been only two patients with perforation, the last one of whom made an uneventful recovery without signs of mediastinitis, due to vigorous coverage with antibiotics and sulfonamides as soon as perforation was discovered. Dr. Stutsman will discuss the treatment of lye burns from an ENT standpoint. We regret that Dr. Burford is on vacation and cannot discuss the surgical treatment.

DR. A. C. STUTSMAN.—I would like to say something about the method of treatment of lye strictures months after the stricture has formed. I would like to emphasize the importance, first, of maintaining the fluid intake of the patient and of doing something about the nutritional status of that patient. That is often a problem and must be attended promptly once the child comes in for observation. The next thing is the diagnosis, and this can be established in two ways: (1) barium swallow, and (2) esophagoscopy. Certainly all patients should have esophagoscopy at the beginning of treatment to determine the amount of stricture and the location and character of the stricture. Once this is done, treatment may follow one of these courses: (1) Bouginage in the direct manner through the esophagoscope. This method is satisfactory in some cases. It is used extensively in some centers, and I think it depends to some extent on the number of strictures and how difficult the esophagoscopy is. I think it is the most dangerous of the methods. There were no cases of rupture by the retrograde method. The one rupture was by the direct method. If the case is such that the direct method is not considered satisfactory, then we use (2) retrograde bouginage. Gastrostomy is necessary in order to use this method of treatment, and serves a double purpose because many children are in a bad state of nutrition, and gastrostomy can be used to re-establish adequately the nutritional condition of the patient. So this method may be used for treatment of the general condition of the body and later for dilatation of the stricture. A string should be introduced into the esophagus and into the stomach as promptly as possible after the patient comes under observation. Much time is lost in getting the string down, and you heard what the varying periods of time required have been. Some of that is due to the fact that we have not been too diligent in trying to accomplish this and lose time. Every effort should be made to get the string down promptly. Lead shot has been mentioned as useful, but it is important to remember that it may serve as a foreign body and block the stricture. After gastrostomy is done and the child has recovered generally, nutrition is adequate, and the string down, bouginage can be started. This is fairly simple. A bougie is pulled through the gastrostomy up through the esophagus and mouth. We start with a small size and increase the size as we go on. The usual thing is to take two or three bougies through at one sitting if possible, the first serving as a test bougie. If it is too tight, we start over.

If retrograde dilatation is not successful, we consider (3) surgical procedures. The esophagus can be exposed at the location of the stricture and the surgeon can guide a filiform bougie through the stricture safely into the stomach

to permit a string to be pulled through. The location of the stricture has something to do with whether or not such surgical exposure would be a fairly safe procedure. It can be done in the upper third; the middle third might produce some danger; it can be done in the lower third. I should have mentioned before that esophagoscopy can be done in the usual way and then retrograde esophagoscopy can be done using an esophagoscope or cystoscope so as to pass the lower third of the esophagus and then from above and under biplane fluoroscopy a filiform bougie may sometimes be passed. All this requires much patience on the part of the physician and understanding on the part of the parents. One must endeavor to be patient with the parents too. It is a long, drawn-out procedure.

DR. PAUL ZENTAY.—I would like to say something about the problems presented here. Twenty-five years ago this fall the first patient in this country was treated with this preventive method by Dr. Wilburt Davison and myself at the Harriet Lane Hospital. This is the first time results obtained here have been summarized. Out of nine patients receiving proper early treatment, seven had no trouble at all. The other twenty-nine had to go through tortures, and you have heard what it means to treat them from above or below. The children coming to the hospital late were extremely emaciated and had other evidences of starvation. Today the problem is a public health problem, and there is no reason why the figures we have here should not be published, so similar tragedies will not occur again. The data should be made known to doctors. One important point in the first examination is that the fact that the child has no burn in the mouth is not significant. There may be a bad burn in the mouth and not much in the esophagus, or there may be nothing in the mouth and a very severe burn in the esophagus resulting in extreme stricture. It is very gratifying that our results are in harmony with those published almost thirty years ago.

DR. PARK WHITE.—Dr. Webb said that in the first case treatment was conservative. She meant treatment was bad. The first patient did not appear at Homer G. Phillips Hospital. At Homer G. Phillips Hospital patients are tubed very quickly, and I think in the early days we were too much afraid of poking a tube into the mediastinum, and hence many patients were deprived of early treatment. At Homer G. Phillips Hospital, economic circumstances, etc., cause us to see many of these patients. The mothers work, and the children have access to lye.

DR. WEBB.—These bougies are not long enough for an adult. At City Hospital, Dr. Ogura had a rather disappointing experience in that he used them on an adult, and after a while a stricture formed. Fluoroscopy with the bougie in place showed that it reached just to the cardia where there was a stricture. On esophagoscopy, scars of the esophagus were seen above the stricture, but the lumen was adequate as far as the tube reached. These children are hard to manage with longtime therapy. They do not cooperate; they do not like to come back. If there is a gastrostomy tube in place, they are more willing to come back.

DR. HARTMANN.—Aside from its academic interest, Dr. Webb's analysis should help guide us in taking the right course at all stages of difficulty. Dr. Webb, have you also come to these conclusions: (1) that our own experiences, together with those already published, point overwhelmingly to the good results that can be obtained with little or no danger from early dilatation, so that every effort should be made to see that the strictures are dilated early; (2) that we should never be lured into a position of false security by being permitted to believe that only the mouth is burned or that the lye was spat out without having gone down to burn the esophagus; (3) that we have to be prepared for two types of failure: (a) stricture developing under treatment—two of ours showed that; (b) the development of stricture in a child with no treatment; (4) that we should be on the look-out for the type of case with injury confined to the lower third of the esophagus, as these are the ones that we should not want to overlook too long? In the others we can try the usual treatment, but this is not doing the best service to the child who has a very serious stricture in the lower part of the esophagus, for, if we are not successful with the usual treatment, it might be impossible to bring up the stomach to the esophagus for anastomosis. We want to get good visualization of the esophagus by the direct method or by the indirect method and feel strongly that thick barium has to be employed or a false conclusion may be reached. To satisfy my curiosity, was it a well-developed stricture that you failed to visualize?

DR. WEBB.—It was in the little girl. It was a well-developed stricture, but the child was hard to handle under the fluoroscope; she cried, and the barium fell through the stricture and could not be seen.

DR. HARTMANN.—It was a short stricture with a narrow lumen, but the material could get by, and did pass so rapidly that you failed to visualize it. With thicker barium, visualization is better; it goes through more slowly.

Also, we learned that in the short time of four weeks following injury very firm scarring can occur that would be hard to dilate. So, if we are on the lookout for only lower third involvement, fairly early operation of the type that the girl had, bringing the stomach up into the thorax, should be considered. In all other types fairly early gastrostomy with attempts to pass the string should be made. If we wait too long, nutrition fails, and it is hard to pass the string. If there is involvement of only the upper third, and gastrostomy and passage of the string and attempted dilatation have failed, then these may be screened out for the surgical tube method. As far as this patient is concerned, our feeling is that we should waste no more time and go ahead with gastrostomy with attempted passage of the string for retrograde dilatation. Dr. Zentay, do you also come to that conclusion?

DR. ZENTAY.—There is no question about it.

DR. ROBERT GARNER.—Dr. Stutsman, how soon is it safe to do esophagoscopy after swallowing lye?

DR. STUTSMAN.—It varies with the child. About a two- to three-week period would be moderately safe.

DR. GARNER.—Are you committing yourself to long-term treatment with mercury bougies? There will be certain cases where children would not have gotten lye into the esophagus. How would you tell which they were?

DR. STUTSMAN.—I think esophagoscopy and barium studies will tell that. Esophagoscopy should be done four to six weeks after it happens if there is some doubt as to the amount of damage to the esophagus.

DR. MIRIAN PENNOYER.—Regarding replacement of the upper third of the esophagus by a tube in certain selected cases, what happens as the child grows? Must we anticipate reoperation and substitution of a larger size tube in a few years?

DR. HARTMANN.—The method of reconstituting an upper esophagus in children has not yet been done, so I cannot answer that. In adults the procedure has been used in patients with carcinoma, and that has not allowed any long-time study of the situation.

Do you really believe, Dr. Stutsman, that if we went on the assumption that the esophagus had been injured and started on a dilatation program as outlined, then went along two or three weeks with no difficulty and wondered if we had to go through the whole program, that we could certainly find out by esophagoscopy if there had been injury?

DR. STUTSMAN.—I think you could to a reasonable degree. I would, however, keep the child under observation.

DR. HARTMANN.—In the second patient, the child swallowed boiler compound and developed stricture despite dilatation. Was esophagoscopy made at any stage, and what were the findings? Dr. Webb felt that at one stage we waited a little too long.

DR. WEBB.—Esophagoscopy was not done on that child until one month after the child had taken boiler compound, and we also began to run into trouble with dilatation from above. I wonder if our mistake was not that we dilated daily for two weeks, and then during the last two weeks when on an every-other-day schedule four days were skipped without dilatation. It was at that time that we first noted trouble.

DR. STUTSMAN.—Do you think that construction of a tube should be delayed until other methods have failed?

DR. HARTMANN.—Yes, because the tube is good only for upper strictures. In the cases with lower stricture you might not be doing the right thing in delaying anastomosis and attempting dilatation first.

To get back to Dr. Garner's question: Are you committing the child to a whole course of dilatation if you are not sure that burn has occurred? Dr. Garner, I would rather see fifty children go through dilatation unnecessarily than have one miss it who needs it, because results are so bad if that happens.

DR. WEBB.—I think prophylactic dilatation should be carried out for two months at least and then if no suspicion of stricture is present, diagnostic esophagoscopy should be done.

DR. HARTMANN.—Is it what you see through the esophagoscope or what you see as a result of barium or Lipiodol instillation that is diagnostic?

DR. STUTSMAN.—I believe esophagoscopy is diagnostic. You see an irregular lumen or evidence of scarring in some places through the esophagoscope as early as five to seven days.

DR. HARTMANN.—So then, if you saw scarring or an irregularity of the lumen, you would go ahead with dilatation.

Case 4. Tetanus

DR. JAMES MCNEIL.—J. G., an 11-year-old white boy, was admitted to the hospital on July 19, 1948, complaining of difficulty in opening his mouth and swallowing and of intermittent attacks of severe, generalized stiffness.

Five months prior to admission he sustained a compound fracture of the left tibia and fibula when struck by an automobile on a country road. He was treated with traction, casts, and penicillin, and the fracture healed uneventfully. He had no history of antitetanic serum or of other tetanus immunization. Nine days before admission his cast was removed, a small draining pressure sore was observed, and the cast was reappplied. No antitoxin was given.

Two days before admission he began complaining of difficulty in opening his jaws and swallowing and of pain through his shoulders and back, particularly when walking. Due to his abnormal gait associated with his fracture, it is difficult to determine if he had any disturbance in walking due to tetanus prior to the onset of generalized tetanic contracture. On the morning of admission, the patient started having intermittent attacks of opisthotonos, complete loss of voluntary muscle control, and moderate respiratory distress. These manifestations became progressively more severe, and it was noted by the parents that they could be precipitated by any ordinary stimulus such as jarring the bed, any sudden noise, or moving the patient.

Physical examination revealed a well-developed, well-nourished 11-year-old white boy who could not open his mouth over one centimeter. His speech was somewhat nasal in quality and difficult to understand. He had multiple skin lacerations over the right foot and leg, an old laceration surrounded by a $\frac{1}{2}$ by 3 cm. area of reaction on the medial aspect of his right elbow, and two small, healed areas beneath his cast which may have been pressure sores. All cultures from these lesions were negative for *Clostridium tetani*. He was extremely restless; his abdomen remained boardlike between tetanic contractions, and, as noted by the parents, any ordinary stimulus precipitated an attack of rigidity.

Treatment consisted of a 70 mg. per kilogram dose of Avertin per rectum which brought about complete muscle relaxation. He was then given a total of 100,000 units of tetanus antitoxin, 50,000 units intramuscularly and 50,000 units intravenously. General precautionary measures such as darkening of the room, no visitors, minimal manipulation, and special duty nurses have been observed. He had been given nothing by mouth and maintained on 1,500 c.c. of intravenous fluids per day. Three hundred thousand units of Duracillin have

been given intramuscularly each day as prophylaxis against pulmonary complications. Sedation sufficient to keep the abdominal muscles relaxed has been maintained with approximately 80 mg. per kilogram of Avertin every four to six hours.

During the first four days in the hospital, the patient had repeated bilateral spontaneous epistaxis and had to be suctioned frequently to keep the respiratory passages open. On the fourth day he aspirated some blood and became very cyanotic. A tracheal catheter was passed, and a large amount of blood was aspirated from the trachea. During the next eight hours he had shifting breath sounds, frequent coughing, and more epistaxis. A tracheotomy was performed, and a large amount of blood was again aspirated from the trachea.

The patient has improved steadily since tracheotomy. He is now being sedated with sodium phenobarbital and a minimum of Avertin. For the past two days he has been fed by means of a stomach tube and is to be started on oral feedings tomorrow.

DR. JEAN V. COOKE.—This is the fifty-seventh patient with tetanus treated in this hospital, and since I had made an analysis of the previous cases, certain features are of interest to mention. The cases can be divided into two groups: (1) twenty-four patients admitted from 1916 to 1932, and (2) thirty-two from 1933 to 1947. Since 1933, we have used the current type of treatment with anesthesia with Avertin to be mentioned later. Previous to that time much less sedative was given, and the results were very unsatisfactory. Of the twenty-four patients treated from 1916 to 1932, twenty died, an 82.5 per cent mortality. In contrast, of the thirty-two patients seen since 1933, only eight have died, a 25 per cent mortality. Of this original group of cases in which there were only four recoveries in twenty-four cases, one patient who recovered was mildly affected and the other three severely, and all received 100,000 units or more of antitoxin. Of the twenty who died, only two received such large doses; the others averaged a dose of about 20,000 units. I do not mean to imply that the large dose of antitoxin was entirely responsible for the recovery or that death could be attributed to the smaller dose. Actually, five died four to twelve hours after admission; eight died the first day, four the second day, one on the third day, so that deaths of these earlier cases were fairly prompt. We believe in retrospect that some of these deaths could have been prevented by prompt, adequate sedation, since our present conception is that death in tetanus in the majority of cases is due to a convulsion or spasm of the respiratory muscles. If this can be prevented, there is a good chance that the disease may be prolonged until the tetanus toxin is oxidized and the stimulation of the muscles ceases.

The various portals of entry are of some interest. In certain cases no wound can be discovered, and it has been suggested that the portal of entry might be through the gastrointestinal tract, although this is rather speculative. In these fifty-six children, thirteen, about 20 per cent, had no demonstrable portal of entry. In the others, several different types of wound were found. The commonest was a laceration (twelve cases), puncture wound (ten cases), wound

from a splinter (seven cases), gunshot wound (six cases), two cases of tetanus neonatorum, one burn from a toy pistol, one following a compound fracture, one following ritualistic circumcision, one in a 9-month-old child following a cut on the lip after a fall out of bed, one following a puncture wound of the palate (the child fell with a stick in his mouth), one from a foreign body in the ear (a piece of coal). It is apparent that a variety of wounds have been followed by tetanus, many of them a small scratch or laceration, and in only a small percentage is it the typical punctured wound. Boys are more susceptible than girls in proportion of 2 to 1. By age, the largest group was in the second 5-year period (5 to 10 years) with twenty-six, while seventeen were under 5 years, and 13 from 10 to 14 years. The diagnosis was usually easily made as the classical signs of stiff muscles, trismus, etc., were usually present. In one child, however, the signs were those of severe, acute encephalitis, and the disease was unrecognized. So far as the incubation period is concerned, there is evidence that the patients suffer more severely the shorter the incubation period, it being assumed that the toxin formed in large amounts is absorbed rapidly and produces symptoms earlier. Actually we did find that most of the deaths occurred in children in whom the incubation period was less than a week, and those in whom it was longer than a week were less severe. Another point of some importance in prognosis is the duration of symptoms before the child is brought to the hospital. When the symptoms appear and progress very rapidly to the point of convulsion, the disease is much more serious than when slight stiffness of the muscles and trismus have been present several days before the patient comes to the hospital.

In about 1933 we started on the hypothesis that we should attempt to prevent convulsions by some powerful sedative, and since that time all the cases have been treated with Avertin except one, which was so mild that no sedative was necessary. Of the remaining thirty-one, eight were fatal, and in almost all of these children death apparently was due to bronchopneumonia, since, as might be expected, patients under such sedation have a tendency to develop pulmonary infection and aspiration pneumonia. Most of the fatal cases were treated before the sulfonamides and penicillin were available. Several children who were fed by gavage developed aspiration pneumonia and at least two died from pneumonia after the tetanus symptoms had subsided. It was apparent that the danger of aspiration could be minimized by giving nothing by mouth during Avertin sedation. Six of the eight deaths were apparently due to pulmonary infection. One child died in a convulsive spasm due to insufficient sedation. One child died two days after admission apparently from respiratory and circulatory failure; since the convulsions were controlled, there was no over-sedation nor any sign of pneumonia. Two children have had tracheotomy as in the one here reported because of aspiration of blood from biting the tongue. One died from bronchopneumonia, and one recovered. We have had no deaths since 1944 and have reason to hope that the chief cause of death, bronchopneumonia, will now be greatly lessened by the use of sulfonamides and antibiotics.

DR. HARTMANN.—I would like to outline therapy given in the past. Here it is fairly easy to agree on principles of treatment; sometimes it is more difficult to carry out details of these principles which are called for. This child was tracheotomized, and I think we overlooked something important. As Dr. Cooke has outlined, it certainly has seemed, from results up to 1932 to the introduction of sulfonamide drugs and penicillin, that just the control of convulsions was a very important thing, and a mortality rate up to 83 per cent was dropping very sharply with introduction of proper anesthesia. I think we would regard treatment this way. We would state that the first thing to do with a child with tetanus would be to get in a large dose of antitoxin to neutralize any further toxin that might be developed and prevent further damage to nerves and muscles, but it is of importance here that you cannot administer large doses of antitoxin in a way to invoke a fatal convulsion. When a child has a severe tetanic convulsion, not only obvious muscles are affected but also the larynx is in spasm, and asphyxiation might occur. The first thing to do is to thoroughly sedate the child and then give intravenous and intramuscular injections without danger of stimulating convulsions. Give immediate anesthesia with rectal avertin and adopt 80 mg./kilogram as the initial dose, expecting almost always to have to add another 20, 30, or 40 mg./kilogram in an hour or two to get the proper degree of sedation. It usually takes 100 mg./kilogram to accomplish that with a child with tetanus. Then go ahead with injection of at least 50,000 units intramuscularly and 50,000 units intravenously. Perhaps just one early administration of antitoxin is enough. Then try to keep the child safely in sedation, so that convulsions will not tend to develop. Here you run into difficulty because you may give too little Avertin or not give it often enough and allow the child to come out so completely that a severe convulsion develops. In one instance such a convulsion seemed to have caused death. On the other hand, if you give it in too large quantity and too often, you run a great risk: the blood pressure falls; pulmonary edema may develop; the cough reflex is abolished; if vomiting occurs, aspiration is easy. Constant observation and expert judgment are needed. Special nurses for twenty-four-hour duty are required. Because it seems that dangerous doses of Avertin will be required in order to prevent too-severe convulsions, you consider adding some other substance similar to the Avertin to cut down its dosage. Try to work out a maintenance dose of phenobarbital as an additional sedative, so that you can give less Avertin. After the first eight to ten to twelve hours one begins to think about that. As to the original cause of tetanus, if there is a puncture wound or an area of infection, deal with it surgically while the patient is under anesthesia. Occasionally excision of such an area of infection is resorted to. If it is an old lesion, a scar or a scratch, and no infection is present, we have felt that no excision is needed. It is necessary then to support these children by artificial methods of fluid and food administration. Fluid is more important than food. For the most part these children are in good nutrition and can stand semistarvation if they do not become dehydrated or have severe changes in metabolism. Ordinary salt solution and glucose solution are indicated early, and the intravenous route by

interrupted method is preferred. Fluid given at deep sedation will cause less discomfort. Gradually add to simple fluids those more complete in coverage of food—one can add Amigen, plasma, albumin, and whole blood when there is a real problem of maintaining nutrition. We feel that with gavage, regurgitation and aspiration are facilitated, so we prefer parenteral feeding. Suppose that despite all these measures, treatment still seems not effective. Suppose convulsions do occur or circulatory failure and pulmonary edema develop, or that there has been aspiration with the probability that the patient will develop pneumonia. Is there anything further to do? On two occasions we were forced to consider tracheotomy, and results were miraculous. In the first child it was discovered that obstruction to one main bronchus had occurred and aeration of the other was not too good, and during a convulsion the child had bitten his tongue and aspirated a considerable amount of blood. We wondered if actually we could do a tracheotomy. As it turned out, we had no trouble at all, and a large blood clot was removed. The child then did beautifully and recovered without difficulty. In this child much the same thing developed following epistaxis. In this instance tracheotomy was carried out sooner. It seems it should be done more often and sooner for prevention of laryngospasm. It keeps the respiratory passages free. Can the respirator really be used after a tracheotomy? This can and has been done during a polio epidemic in Minneapolis.

DR. JOSEPH OGURA.—In this patient the problem consisted of pooling of blood from the epistaxis with mucus in the hypopharynx, and with the difficulty in swallowing due to spasm of the pharyngeal muscles and the dropping back of the tongue, laryngospasm, and poor cough reflex and atelectasis occurred. The problem then was similar to those in bulbar polio where, because of laryngeal anesthesia and degeneration of the cells in the nucleus ambiguus, there was likewise aspiration of secretions into the trachea. A tracheotomy was, therefore, necessary in this patient, not only for airway but for aspiration of secretions from the tracheobronchial tree.

What are the methods of therapy other than tracheotomy?

(1) *Nasopharyngeal tube by Pearson.* Obviously this method will not take care of the laryngospasm that is present.

(2) *Endotracheal tube* would be of little value inasmuch as it must remain in the larynx much too long with subsequent laryngeal edema.

(3) *Intubation.* Secretions will be aspirated through the tube.

While preoperative bronchoscopy² would be desirable prior to tracheotomy, it was not done because (1) it would stimulate the patient unduly, which we were trying to avoid; (2) there would be difficulty in getting the head in the proper position because of opisthotonos.

Types of Tracheotomy.—It has been said that a high tracheotomy would be more advisable if it became necessary to place the child in a respirator. By definition, a high tracheotomy is an opening above the thyroid isthmus, a low tracheotomy beneath that. A high tracheotomy usually involves going through tracheal rings No. 1 and No. 2. This is not desirable for several reasons: (1)

the tracheal ring would ride on the cricoid. The cricoid is a completely circular cartilage which can be easily damaged when the perichondrium is involved by inflammation. A perichondritis would result. If the inflammation extends forward, a laryngeal stenosis would result. The cords elasticus beneath the mucosa, when involved with inflammation, will result in a cicatricial stenosis. If rings No. 2 and No. 3 are entered, usually this difficulty is not encountered. It is preferable to enter rings No. 3 and No. 4 or lower.

In the Minneapolis bulbar polio epidemic when tracheotomy was done and it was necessary to place the child in a respirator, a high tracheotomy was not done. In their series of bulbar polio cases, in fifteen out of seventy-five tracheotomies thick gray secretions were sucked up into the tracheotomy wounds. In this case, bloody mucus was obtained on opening the trachea. Dr. Holt in Minneapolis devised a method by which a tracheotomized patient could be placed in a respirator. The ring of the respirator into which the head and neck protrude was recessed 3 to 4 inches inward. A funnel rubber sleeve was fitted on this recessed ring and fitted low on the neck. This recessed rubber sleeve low on the neck was held inward into the respirator by a curved metal bar which was attached to the respirator. An additional device was evolved by which there is a three-way inlet which fits onto the tracheotomy tube: an oxygen inlet with a one-way trap valve and an outlet valve; the third outlet was kept closed and used for suctioning. By this method oxygen would be in the closed system and can be humidified to the proper percentage and temperature. Dr. Elam of our Department of Thoracic Physiology has kindly let me show you this apparatus which, he believes, is superior to the apparatus which was used in Minneapolis. It consists of the double rubber sleeve which fits much more snugly on the patient and is held inward by a metal bar which protrudes over the chest of the patient. I would like to point out at this time one important study published in *Pediatrics*, June, 1948, by Goule and Elam. They made oximetric studies using a photoelectric cell to the ear lobe in tracheotomized patients and demonstrated that with the respirator in use, intermittent use of suction through the tracheotomy may reduce the oxygen saturation from a normal of 95 per cent or higher down to an hypoxic state. While suction in bulbar polio or in any tracheotomized patient who needs a respirator is necessary, it should be used cautiously and judiciously.

DR. HARTMANN.—Would you try to make the opening in the second and third rings?

DR. OGURA.—Yes.

Case 5. Growth Failure Associated With Renal Insufficiency

DR. NORMAN HANKIN.—R. K., was 2½ years of age. This child's first admission to St. Louis County Hospital was on Nov. 1, 1946, at the age of 9½ months. Chief complaints then were cough for ten days, drowsiness and dyspnea for the past seven days, and anorexia for the past twenty-four hours.

The past history revealed that he was born prematurely at home in Pacific Mo., and was cared for at a Washington, Mo., hospital for one month. At the age of 2 months he developed pneumonia and returned to the Washington Hospital where he remained for a month. He seemed to do well, however, until this present admission. The mother was found to have pulmonary tuberculosis when the baby was 4 months of age and was sent to a sanatorium.

Pertinent physical findings in November, 1946, were a greatly retarded, pale, dehydrated infant who was in moderate acidosis and running fever of 102.4° F. At that time a mass could be palpated in the right lower quadrant. Laboratory findings were as follows: carbon dioxide, 26 volumes per cent (11.8 meq. per liter); nonprotein nitrogen, 68 mg. per cent; white blood cells, 14,000; stab cells, 3; segmented, 9, lymphocytes, 86; monocytes 2.

He was treated for his acidosis, placed on chemotherapy and penicillin because of a coincident otitis media (right ear). The persistence of symptoms and presence of the abdominal mass led to I.V. pyelograms which were unsuccessful on two occasions. On Dec. 18, 1946, a cystoscopy was done, and some congenital urethral valves were removed. Because of a persistent finding of pyocyanus in urine cultures first noted on Jan. 17, 1947, streptomycin was started.

Retrograde pyelography on Feb. 14, 1947, revealed hydronephrosis on the right with bilateral upper ureteral stricture.

On Feb. 24, 1947, the right kidney was explored and found to be enlarged, hard, and nodular with numerous small cysts visible on the surface. The pelvis was dilated tremendously. There was also a stenosis of the ureter about one-half inch distal to the pelvis. This stenotic portion was excised and the lower portion of the ureter anastomosed to the pelvis. A nephrostomy was then done.

The patient had a satisfactory postoperative course, and on March 3, 1947, the left kidney was explored. It was found to be atrophic and nodular, and numerous small cysts were noted on its surface. There was an atresia of the proximal portion of the left ureter. A left nephrectomy was done.

The patient ran a persistent fever, elevated nonprotein nitrogen and low carbon dioxide but was finally discharged after five and one-half months on May 23, 1947. He was placed on 15 c.c. molar sodium lactate three times a day by mouth and was to be followed in the out-patient department.

Since then, this patient has had six hospital admissions for treatment of upper respiratory infections complicated by moderately severe acidosis, anemia, azotemia, and hyperphosphatemia. Between Jan. 24, 1948, and March, 1948, he developed multiple fractures of the right arm, left femur, and left tibia. Each of these admissions has required rather energetic treatment, and retardation of growth and development has been noted in each instance. He has always been discharged on oral molar lactate, calcium, and vitamin D.

This present admission was on July 7, 1948, after an interval of three months with a history of having refused solid foods for the past three to four weeks together with some vomiting. For the past three to four days he has had a rhinitis, nonproductive cough, rapid breathing, skin eruption, and fever.

Physical examination revealed a poorly nourished, dehydrated, greatly retarded, pale infant with acidotic type of respirations. The skin had some small papules (3 to 5 mm. in diameter) scattered over the entire body, especially over the forehead. There was frontal bossing, and the veins of the forehead were prominent and distended. The gingiva of both jaws were greatly hypertrophied. There was a bilateral otitis media present. The spleen was palpable about one fingerbreadth below the left costal margin. He was unable to sit up or talk. There was also some questionable clubbing of the fingers and toes.

The initial carbon dioxide was 25 volumes per cent (11.3 meq. per liter), and the nonprotein nitrogen was 156 mg. per cent. He was treated for acidosis and dehydration with 1/6 molar lactate, and also placed on antibiotics. At the present time he is relatively afebrile and is being maintained on oral molar lactate, calcium lactate, and aluminum hydroxide. He has also been given two transfusions.

Laboratory Data on Last Admission

July 22, 1948	WBC, 8,800 RBC, 1,510,000 Hemoglobin less than 7.5 Gm. N.P.N., 156 mg. per cent CO ₂ , 25 vol. per cent (11.3 meq. per liter) Serum calcium, 7.6 mg. per cent Serum phosphorous, 12.0 mg. per cent
July 23, 1948	CO ₂ , 52 vol. per cent (23.1 meq. per liter)
July 24, 1948	N.P.N., 84 mg. per cent Creatinine, 4.1 mg. per cent
July 26, 1948	Serum cholesterol, 227 mg. per cent
July 27, 1948	WBC, 9,850 RBC, 2,980,000 Eosinophiles 1, segmented 24, lymphocytes 68, monocytes 7 Hemoglobin, 8.5 Gm.
July 28, 1948	Alkaline phosphatase, 18.8 units Phosphorus, 6.5 mg. per cent Serum calcium, 9.4 mg. per cent Total proteins, 6.38 Gm. per cent

X-ray Studies.—(1) Retrograde pyelogram, April 18, 1947 (Fig. 5). The opaque catheter on the right extends to the ureteropelvic juncture. There is a marked dilatation of the pelvis of the right kidney with a constriction at the ureteropelvic juncture. The condition is due to a marked hydronephrosis of the right kidney.

Showing nephrostomy tube in place, March 14, 1947 (Fig. 6). Examination of the right kidney after injection of opaque solution reveals some dilatation of the superior infundibulum, but the pelvis of the kidney is much smaller, and the minor calices are much smaller than at previous examination.

Skull film, Dec. 12, 1947 (Fig. 7). Examination of the skull reveals a pronounced miliary mottling involving all of the bones. There is definite thickening of the cranial bones, especially in the frontal and posterior parietal regions and to some extent in the occipital region.

Left leg, Feb. 9, 1948 (Fig. 8). There is a transverse fracture of the left tibia with no displacement of the fragments.

Showing calcification of soft tissues, Dec. 6, 1947 (Fig. 9). Both lower extremities are shown.



Fig. 6.



Fig. 5.



Fig. 7.

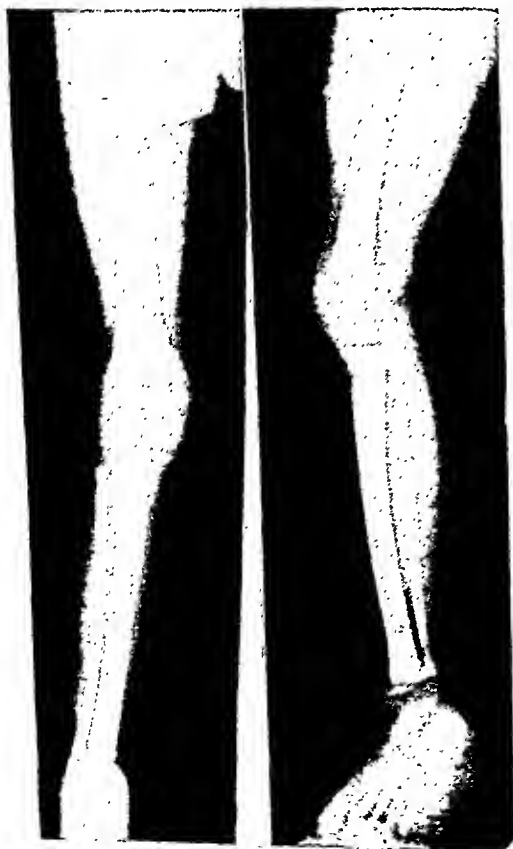


Fig. 8.



DR. LEO GOWEN.—We are presenting this child as a case of primary renal insufficiency with secondary compensatory hyperparathyroidism. The renal insufficiency is due to polycystic kidneys; an atrophic, polycystic, functionless left kidney has been removed, while on the right side the ureter was found stenotic and dilated proximally, with resultant hydronephrosis and stasis infection. Surgery has relieved the obstruction in the right ureter, and antibiotics and improved urinary drainage have controlled the infection. That portion of the remaining kidney which functions does so poorly as manifested by the high degree of nonprotein nitrogen retention and hyperphosphatemia. A poor prognosis is to be seen in the very low and still decreasing values of the urea clearance tests and the increasing degrees of azotemia and phosphatemia and the persistent acidosis. The latter seems due chiefly to failure of reabsorption of fixed base (chiefly sodium) because of damaged tubules, but is also contributed to by failure of excretion of fixed anion, particularly phosphate, which results in hyperphosphatemia. There is to be noted some reciprocal fall of serum calcium, but without tetany, probably because of the relatively increased calcium ionization brought about by the acidosis (increased H^+ ion concentration of the blood). Hyperparathyroidism, secondary it is usually thought to the hypocalcemia, probably accounts for the depletion of the calcium stores of the body. The soft tissue storehouses of calcium are thought to be called upon first until depleted, and then the hormone turns to the base of the skeletal structures. In bone there is considerable sodium which first may be used to neutralize ordinary acids of metabolism. The calcium of the matrix of bones is then drawn into the blood serum. As a result there is a generalized decalcification of the skeleton similar to atrophic rickets. If epiphyseal growth occurs, as did in this child, bending and distortion of the long bones may occur, giving rise to what is termed by some "florid rickets." Finally a fuzzy appearance of the bone with cystic change may be noted, along with calcification in the soft tissues, which is usually referred to as "woolly bone changes," osteitis fibrosis cystica, or osteoporosis.

Renal "dwarfism" has been noted in five different conditions of renal insufficiency: (1) chronic glomerulonephritis, (2) congenital polycystic kidneys, (3) pyelonephritis, (4) renal hypoplasia, (5) hydronephrosis.

Various names have been used to designate the status of this child's syndrome; viz.

(a) Renal rickets, which is not adequate, for skeletal changes are not those of rickets but of an osteoporosis.

(b) Renal dwarfism, which does not describe the picture, for "dwarfism" implies only smallness of size, whereas deformities are also present.

(c) Renal infantilism would only be of some value for those patients who were in infancy.

(d) Osteitis fibrosa cystica which term suggests an inflammatory etiology, whereas the term renal hyperparathyroidism with osteoporosis fibrosa cystica, indicates not only the bone pathology but also the etiologic systems involved, and implies the sequence of pathologic physiology.

Important in caring for this child have been: (1) combating infection and avoiding reinfection; (2) frequent transfusions because of hypoplastic bone marrow; (3) furnishing large amounts of water to counteract effects of polyuria; (4) replacing sodium, which is constantly being lost via urine, by giving sodium lactate between meals; (5) giving calcium orally (after meals with the hope that it may be absorbed better in an acid pH of the small intestine); (6) giving adequate vitamin D and orange juice to favor the absorption of calcium; (7) avoiding high fat in the diet; (8) providing high alkaline ash foods; (9) using aluminum hydroxide in addition to calcium to lessen the absorption of phosphate from the intestine; (10) replacing chloride ion when lost by vomiting; (11) administering sufficient lactate to control acidosis.

Because of the findings in this case of polycystic kidneys associated with infection and chronic renal insufficiency and acidosis, hyperphosphatemia, hypocalcemia, and increased phosphatase activity, with generalized osteoporosis and deformities without hypertension, we feel that the patient conforms to the diagnosis of renal hyperparathyroidism with osteoporosis fibrosis cystica.

DR. ALEXIS HARTMANN.—This is an amazing case, a typical example of growth failure associated with renal insufficiency and very profound disturbance of bone growth. When Dr. Gowen enumerated the different renal causes for failure of development, I thought of a sixth one which we have seen—nephrocalcinosis. At least four of the causes are here: (1) polycystic kidney, (2) hypoplasia, (3) persistent infection, and (4) bladder neck obstruction with hydronephrosis. We are pretty sure that there is no glomerulonephritis, but not so sure that nephrocalcinosis is not also present.

One question is of interest and fundamental in arriving at a conclusion. First attempts made to explain the decalcification of bones were along lines of altered acid-base balance, and it was first assumed that chronic acidosis developed and led to abnormal excretion of cations from the body, largely sodium and potassium, but later calcium and magnesium. That led to rickets or bony changes called rickets and which resembled changes of hyperparathyroidism. One interesting case in particular was studied by Boyd and Stearns. They reported a case of persistent rickets with chronic acidosis as the only apparent cause, where alkali administration alone was successful in controlling the rachitic process. Recently, however, it has been demonstrated that ordinary vitamin D rickets can be treated quite successfully without vitamin D but by dietary measures which provide intestinal acidity with alkaline ash. Only two buffer substances are effective, citric acid and sodium citrate or tartaric acid and sodium tartrate. Lactic acid and sodium lactate are not very successful.

Do you have any evidence that after prolonged alkalization any improvement in the skeletal process took place? This child has received 200 c.c. molar sodium lactate daily or almost 30 c.c. kilogram. Dr. Gowen, when you tested the pH of urines with nitrazine paper, you very often found it to be very alkaline, and fresh urines approached a pH of 8. This is very interesting

and important to verify, because our concept would be that any child with only one kidney, and that so badly involved, would not have the ability to concentrate sodium bicarbonate any more than he would have the ability to concentrate anything else. It would be well to determine the carbon—dioxide content of freshly passed urine to see what there is in the way of sodium bicarbonate in the urine. Is there any evidence that alkali therapy has changed the skeletal picture in this child?

DR. GOWEN.—I do not know whether I can answer that, Dr. Hartmann.

DR. HARTMANN.—Well, that would take considerable study. From your plates, such therapy would not seem to have changed it. I think these skeletal changes are principally due to the hyperparathyroidism.

DR. PETER HEINBECKER.—I wish to suggest briefly a possible endocrine basis for the dwarfism exhibited by this child. Normally there are three types of cells in the glandular division of the hypophysis, existing in a balanced relationship. Two of these, the eosinophiles and the basophiles, are secretory. The eosinophile cells are the source of the growth hormone. It is accepted that the hypophysis, as the master gland, is trophic or inhibitory to the other endocrine glands. What is not realized so generally is that it is, in itself, subject to modification by these same endocrine glands. Six months after adrenalectomy with maintenance on deca (desoxyeorticosterone acetate) pellets there has resulted a marked disappearance of eosinophiles. The growth-stimulating potential of such an hypophysis would be reduced greatly. In support of this is the evidence that pups with only enough adrenal tissue left to support life show a marked retardation of growth. Likewise it has been shown in our laboratory that the hypophysis of a dog with one kidney removed and the other wrapped in silk to produce hypertension, shows a great increase in eosinophile cells and a decrease in chromophobes. The width of the adrenal cortex of such a dog is widened. Similar effects are produced during the period of hypertension when one kidney is left intact and the other wrapped in silk. Presumably a lessening of blood flow to the normal renal tubular tissue is responsible for the release of the hormone (renin?) when kidneys are so treated. The hormone released from the kidney effects an increase in the number and the secretory capacity of hypophyseal eosinophile cells.

In this patient there is evidence that the renal tubules are functionally depressed, probably greatly reduced in number. As a consequence it is reasonable to suspect that they would secrete an inadequate amount of the hormone believed essential for the maturation of hypophyseal eosinophile cells. The diminution in number and effectiveness of such cells would be expected to interfere with normal growth. It would lessen the efficacy of the adrenal cortex. Many of the chemical disturbances exhibited by this child suggest adrenal cortical deficiency. The failure of the growth hormone would decrease the growth of the other hypophyseal cells, including the basophiles. These cells, in other studies, have been found to be inhibitory to the parathyroid glands. Consequently, their decrease would permit overaction of the parathyroid glands.

In summary, then, on the basis of experimental evidence and on evidence presented here this morning, it is suggested that a marked defect, primary in the renal tubules, could be expected in the young to cause changes in the hypophysis, in the adrenal glands, and in the parathyroid glands, of a nature and direction to produce the clinical picture exhibited by this child.

DR. JOSEPH JAUDON.—If pituitary dwarfism is based on overaction of the parathyroid and underaction of the adrenals with contrarenal enlargement of that kidney after being wrapped in silk, do you have other evidence of increased growth of other tissues other than the adrenals and kidney?

DR. HEINBECKLER.—Not ordinarily, except where you get acromegaly.

Psychologic Aspects of Pediatrics

BREAST FEEDING

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ALTHOUGH it is generally agreed by obstetricians and pediatricians that breast milk is the preferred food for infants, the incidence of breast feeding is declining.¹ Moreover, the duration is becoming shorter. In England and Wales 80 per cent of the babies born in hospitals and 95 per cent of the babies born at home are entirely breast fed. Whether the infants are born in the hospital or at home, by the end of three months only 50 per cent and at the end of six months only 40 per cent continue to be breast fed.^{1, 2} Statistics on breast feeding in this country would show a much lower incidence.

The reasons for the decline in breast feeding are numerous. Perhaps most important is the ease and success of artificial feeding. Many women have an aversion to breast feeding, looking upon it as an activity suited only for lower animal forms. There is a false impression that breast feeding is confining. Hospital delivery with the premature use of artificial feeding before the breast milk comes in and the early resort to complementary feeding contribute to the failure of maternal nursing. In many hospitals breast feeding is discouraged as it interferes with the "routine" of the nursery.

In the early days of artificial feeding, efforts were directed toward devising a milk mixture which would duplicate in chemical composition the mother's milk. With this idea in mind, cow's milk was diluted to reduce the concentration of protein, and sugar was added to raise the carbohydrate content. By using "top milk" for dilution the concentration of fat was maintained at the level of mother's milk. It was quickly discovered that the differences between the two milks were much more diverse and subtle than had been originally suspected. But, despite this, babies thrived on the artificial mixtures and, with the years, the effort to simulate breast milk has been abandoned. It has gradually come to be accepted by many that, great though the differences between human and cow's milk may be—and the number of differences being discovered is growing—cow's milk is just as good as human milk as a food for infants.³ However, the criteria of adequate feeding are still not well established and the significance of the metabolic differences between the infants receiving the two milks have yet to be determined.

More recently, interest has shifted to the psychologic aspects of breast feeding and there are some who consider that the emotional value of this procedure represents the principal, if not the sole advantage of maternal nursing. With this in mind they advocate duplicating as nearly as possible in artificial feeding the method of holding the baby, cuddling, etc., as is done during breast

feeding. These maneuvers are analagous to the early attempts at modifying cow's milk to make its composition similar to that of human milk and, again, assume a knowledge of the numerous factors implied in the breast-feeding situation which is not justified.

DIFFERENCES BETWEEN HUMAN AND COW'S MILK

It is not our intention to present a detailed review of the differences between human and cow's milk. Excellent studies along this line have been recently published by Maey and associates.⁴ We wish to mention here only certain differences, recently discovered, which illustrate further the complex ways in which the two milks differ.

Protein.—The total protein content as well as the proportion of casein to lactalbumin varies in different milks. Cow's milk contains approximately 2.8 per cent casein and 0.5 per cent lactalbumin; human milk 0.5 per cent casein and 1.0 per cent lactalbumin. Williamson⁵ has shown that, if cow's milk is diluted to make the total protein content equal to that of human milk, noteworthy differences between the character of the proteins remain. Human milk contains three times as much cystine and a larger amount of tryptophan than does the diluted cow's milk. On the other hand, the diluted cow's milk proteins contribute over one and one-half times as much methionine and about 20 per cent more histidine, threonine, and valine than the human milk proteins.

Recent studies indicate that the behavior of casein of human and cow's milk differs.⁶ By means of electrophoretic analysis it has been possible to separate casein into two or possibly three fractions of different chemical composition. The relative amounts of these fractions differ in human and cow's milk. Moreover, in vitro digestion experiments using pepsin, trypsin, and human adult gastric juice, show a considerable difference in the digestibility of casein, the cow's milk casein being more readily and completely hydrolyzed than that of human milk.

Fat.—Both human and cow's milk contain about 3.5 per cent of fat. Hilditch and Mara⁷ have recently shown that the composition of human milk fat differs from that of butter fat particularly in the fatty acid content. Human milk fat contains about 7 per cent linoleic acid, whereas there is little or none in cow's milk. This is one of the unsaturated fatty acids which is essential for the nutrition of rats.⁸ It has also been shown that there is a relationship between the metabolism of fats and lactose, the utilization of the sugars apparently being dependent on the presence in the diet of certain fatty acids.⁹

PHYSIOLOGIC DIFFERENCES BETWEEN BREAST- AND ARTIFICIALLY-FED INFANTS

Nitrogen Retention.—Catherwood and Stearns¹⁰ have shown that the proportion of ingested nitrogen which is retained by infants receiving human and cow's milk is about the same, but since cow's milk contains about twice as much protein, infants receiving cow's milk retain a correspondingly larger amount of nitrogen. They, therefore, have a relatively larger store of tissue protein than breast-fed babies, some of it occurring as muscle. This is of doubtful

value. Jeans¹¹ has shown that, when cow's milk is diluted so that nitrogen retention is reduced to equal that of a breast-fed infant, tissue turgor is poorer and motor development is impaired. Undoubtedly unknown factors in the nature of the proteins of cow's and human milk are involved. The difference in protein retention may be related to the different rates of gain in weight of infants fed breast and cow's milk. Faber and Sinton¹² have shown that, during the first three months of life, breast-fed infants show a significantly better mean weight gain than bottle-fed infants. Later, artificially-fed infants gain more rapidly and this superiority becomes progressively greater up to the time of weaning.

Carbohydrate Metabolism.—Lactose is the sole carbohydrate of milk; human milk contains about 7 per cent and cow's milk 4.5 to 5 per cent. Aside from its value as an energy yielding constituent, it may, by its effect on intestinal microflora, affect the synthesis of various nutrients.¹³ Lactose promotes the absorption of calcium and phosphorus, presumably because of its influence on the acidity of the gut contents. It is generally assumed that the lactose of human and cow's milk behaves in the same manner, but recent observations of Natelson, Kramer, and Sherman¹⁴ indicate that raw mother's milk feedings cause higher blood sugar rises than do similar amounts of lactose in evaporated milk or in raw cow's milk.

Calcium and Phosphorus Retention.—Cow's milk contains, on the average, about four times as much calcium and about six times as much phosphorus as human milk. About two-thirds of the phosphorus in cow's milk is excreted by the infant in the urine. Though the percentage of ingested calcium and phosphorus retained by infants receiving cow's milk is smaller than that retained by infants on mother's milk, the actual amount stored is greater. As a result the percentage composition of infants receiving cow's milk is higher in calcium and phosphorus than that of breast-fed infants. Stearns¹⁵ has shown that during early infancy, when a baby is fed wholly on the breast, the concentration of calcium in the skeleton decreases rapidly and probably does not reach the birth value before the first birthday. This does not mean that the infant is in negative calcium balance but probably indicates that the newborn infant has stored calcium in the skeleton. When, on the other hand, cow's milk is given, a smaller decrease of calcium concentration in the skeleton occurs and several weeks after birth the concentration starts to rise. The significance of these differences is not clear. While it is true that the linear growth of babies fed a standardized cow's milk formula is related to the amount of calcium retained, the breast-fed baby shows excellent linear growth despite the much lower calcium retention and grows at a definitely greater rate than the artificially-fed baby with the same calcium retention.¹⁶ There is no evidence to show that the baby who stores more calcium has any nutritional advantage.

It is of interest that, despite the greater retention of calcium and phosphorus by infants receiving cow's milk, rickets is likely to be more severe among them and tetany much more common. In neither human nor cow's milk have important quantities of vitamin D been found. Perhaps the various relationships of the components of human milk are such that calcium and phosphorus

are more efficiently utilized from this food than from cow's milk. Harris and Bunker¹⁷ have suggested that there may be a specific superiority of the vitamin D content on mineral interrelationships in human milk.

The tetanogenic property of cow's milk has been known for many years and has been attributed to its high phosphorus content. Finkelstein¹⁸ was able to allay the symptoms of tetany by substituting human milk for cow's milk in the diet of affected infants. Bakwin¹⁹ has shown that the feeding of phosphorus to newborn infants leads regularly to a reduction in the serum calcium and he suggests that the early feeding of cow's milk is a factor in the pathogenesis of tetany of the newborn infant.

Vitamin C Retention.—Raw cow's milk under market conditions contains between 1 and 2 mg. of ascorbic acid per 100 c.c. and pasteurized milk about one-half this amount. This compares with from 3 to 4.5 mg. per 100 c.c. in human milk. It appears that breast-fed infants utilize ascorbic acid better than artificially-fed infants. Snelling²⁰ found higher ascorbic acid levels in breast-fed infants than in artificially-fed infants receiving equivalent amounts of vitamin C in orange juice. The possible reasons for this are that breast feeding enhances the absorption of vitamin C or that the continuous administration throughout the whole day allows for more complete absorption. Bakwin²¹ has also reported that the artificially-fed infant requires from 75 to 100 mg. of vitamin C daily to get the same blood levels as the breast-fed infant. Dann²² has shown that premature infants receiving boiled human milk retain a larger part of a "saturation" dose of ascorbic acid in their tissues than do infants given cow's milk. She offers the hypothesis that the increased daily requirement of vitamin C is related to the high level of protein from cow's milk. This explanation is in accord with the work of Levine and his co-workers²³ who have shown that ascorbic acid is concerned with the intermediary metabolism of aromatic amino acids.

Resistance to Infection.—There is a great deal of evidence to show that breast-fed babies are less prone to gastrointestinal disturbances and respiratory infections than artificially-fed infants. The frequently quoted work of Grullee and his associates²⁴ clearly indicates the superiority of breast feeding in this respect. In a study of 26,061 babies under the care of the Infant Welfare Society of Chicago, the incidence of infections of all types in the breast-fed group was 37.4 per cent as compared to 63.6 per cent in the artificially-fed group. Of the breast-fed group, 28 per cent suffered from a respiratory infection of some type as compared to 37 per cent of the artificially-fed; 5.2 per cent of the breast-fed group had various gastrointestinal disorders as compared to 16 per cent of the formula-fed infants. Of 218 deaths occurring in this group 15 or 6.7 per cent were in the breast-fed infants and 144 or 66.1 per cent in the artificially-fed group. Breast feeding apparently gave a much greater immunity to infection than artificial feeding. These findings have been confirmed by other investigators. Ebbs and Mulligan²⁵ examined the records of 1,500 consecutive admissions of babies under 12 months of age admitted to the Hospital for Sick Children in Toronto for various infections. Of this number only 15.1 per cent were wholly breast fed, 29.1 per cent had been breast fed for

at least six weeks, and 55.7 per cent were artificially fed from birth. The incidence of breast feeding among these 1,500 infants with infections was less than half the incidence of breast feeding in the well-baby clinics in the city. Smellie²⁶ reported 375 infants below the age of 9 months with diarrhea. Only 154 or 41 per cent had been breast fed for a month or more. The mortality rate in this group was 25.9 per cent, which contrasts with a mortality rate of 76.6 per cent in those who never had been breast fed. Robinson²⁷ studied 240 infants for a period of twenty months, noting the gastrointestinal disturbances and rashes following different feedings. The breast-fed infants had the lowest incidence of diarrhea and rash. Stevenson³ analyzed the records for the first year of life of 263 infants, of whom 95 were breast fed for three months or longer. He found a higher incidence of respiratory infections among the artificially-fed infants during the second half year of life (1.43 respiratory infections per artificially-fed infant and 0.95 respiratory infections per breast-fed infant). There was no significant difference in the amount of diarrhea and miscellaneous infections between breast- and properly artificially-fed babies.

Diarrhea of the Newborn Infant.—According to Rice and his associates²⁸ the breast-fed is about as susceptible as the artificially-fed infant. However, they mention that it is routine practice in hospitals to give breast-fed infants some form of additional food or fluid during the first week. Therefore, the rubber nipple as a source of infection cannot be ruled out. Cron and co-workers²⁹ describe an epidemic of diarrhea in a nursery. Of this group eighteen of twenty-five babies being formula fed died. Six babies who received breast milk plus formula and eight more who obtained breast milk after having been on formula for three or four days either did not contract the disease or, if they did, survived their illness. Ormiston³⁰ describes an outbreak in which six out of fifty-one sick infants entirely breast fed died, contrasted with ten out of thirty given cow's milk with or without breast milk. Sakula³¹ reports eighteen newborn infants in a nursery who contracted gastroenteritis, of whom fifteen died. The outbreak was confined to bottle-fed infants.

It is true that the technique of breast feeding as compared with artificial feeding allows fewer channels for infection of the infant. However, it seems that breast feeding gives the infant an added measure of protection against both respiratory and gastrointestinal infections. The mechanism for this is not clear. The antibodies of human serum are contained mainly in the gamma globulin fraction. Longworth and his associates³² have shown that both the absolute and relative concentrations of fetal gamma globulin are higher than either the normal or maternal value. Placental transmission of antibodies and not breast milk is responsible for this. Investigations have shown that colostrum is incapable of increasing the level of diphtheria antitoxin in the blood of infants.³³ However, there has been little work done on the possible transmission of virus antibodies through colostrum or milk. In this connection it is of interest to note that Berry and Slavin³⁴ have shown that mice could be passively immunized through the mammary route against infection with herpes virus. This naturally acquired immunity declined rapidly when suckling was interrupted. Whatever the mechanism may be, it is obvious that breast feeding.

even though it be for a short period, offers the infant some degree of protection against gastrointestinal and respiratory infections.

Eczema.—Grulee and Sanford²⁵ have shown that the general incidence of infantile eczema is lowest in breast-fed infants. In the partially breast-fed infants, eczema was twice as frequent as in the breast-fed, and in the artificially-fed, seven times as great. There is as yet no conclusive evidence for demonstrating a causal relationship between sensitization of the newborn infant and the passage of proteins through the breast milk.²⁶

PSYCHOLOGIC ASPECTS OF INFANT FEEDING

The interrelationships which are set up between mother and child during the early days and weeks of life set a pattern which is important for the later development of the child. The mother who nurses her baby establishes, at an early date, an intimacy with her child which makes further relationships with him easy and natural. Czerny, a strong advocate of breast feeding, stated that "between the person (who nurses the baby) and the child those relationships develop which are most highly valued when they exist between parent and child. For the child fed by a wetnurse or a nurse, the mother remains a stranger despite the blood relationship, and the less often the infant sees the mother the stronger becomes the estrangement. The mother who does not feed the child herself creates, already in the first year of life, a barrier between herself and the child which is never completely removed."²⁷

Breast-feeding provides the mother with a sense of satisfaction and a sense of achievement which is not readily obtained otherwise. In no other way can she so well demonstrate her indispensibility to the child. The mother who nurses her baby has him at her side in the hospital five or six times a day. The rooming-in system, by which the mother is permitted to have the baby in her room, loses much of its value if breast feeding is not established, since the benefit derived from the early nearness of the baby is not continued. These considerations are especially important when the mother has strong interests, business, professional, or social, outside the home.

For the baby, too, breast feeding provides emotional satisfactions which appear to be highly important to him. The newborn infant is endowed with a fairly well-developed set of emotional responses. These responses must be elicited by stimuli applied from without through the senses since the newborn infant, lacking cerebral power and experience, is unable to originate emotionally charged situations. Though all his senses are developed and functioning, vision means little to him since, to a very large degree, the interpretation of visual stimuli requires experience. The same is true of auditory stimuli, although here the sound of a cooing voice seems to be soothing. The other senses, smell, taste, the skin sensations, and muscle balance require no experience and appear to be highly meaningful to the young baby. He is readily quieted by warmth, by patting and stroking, and by being allowed to suck. These satisfactions are provided automatically while feeding at the breast. How vital they are for the welfare of the young baby is seen in those cases where the infant is

deprived of such stimulation, as, for example, when hospitalization becomes necessary. In this situation babies wilt quickly and, if deprived for an extended period, many die.³⁵

Infants receiving breast milk more readily regulate their intake than do those on cow's milk. The cautious physician, aware of the danger of intestinal upset during the early weeks of life, will hesitate to give the large amounts of food often required by the infant at this time.

It is not our viewpoint that all babies who are breast fed will grow up to be happy adults or vice versa. We do feel, however, that it is one step, and an important one, in establishing proper interrelationships between mother and child, and in providing suitable outlets for the young baby's budding emotional needs. In addition, under proper circumstances, it supplies a satisfying experience for the mother.

In advising breast-feeding, care must be taken not to stress its importance to such a degree that the mother will feel herself inadequate or blameworthy if it becomes impossible for her to nurse her baby.

SUMMARY

A survey of available data shows that the reaction of infants to human and cow's milk differs in many respects. The differences are reflected in shape of the growth curve, in the amounts of nitrogen, calcium, and phosphorus which are retained, in the plasma vitamin C levels, in the response of the blood sugar to lactose ingestion, in the incidence and severity of vitamin D deficiency disease and eczema, in the incidence of tetany during the newborn period, and in the frequency of respiratory infections. It is not our intention to present these data as evidence of the superiority of human over cow's milk in feeding babies, although the lowered incidence of respiratory infections and severe eczema in the breast-fed infant is a very real, practical consideration. Reasoning from the meager available information, it would appear that breast feeding is superior to artificial feeding from the psychologic viewpoint.

In the last analysis, the choice of one or the other method of feeding stems from a general attitude. The physician who is impressed by the remarkable adaptability of the human organism will, whether giving advice in the care of a well child or in ministering to the sick, interfere minimally with natural processes. We have erred too often in the past.

This is not meant to minimize in any way the enormous value of artificial feeding for those infants who, for one reason or another, are unable to be fed at the breast. We do feel, however, that artificial feeding should be reserved for the instances where an honest attempt at breast feeding has failed.

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Comments on Current Literature

BRUCELLOSIS

THE August (1948) issue of the *Annals of Internal Medicine* carries an instructive discussion of human brucellosis by Dr. Wesley W. Spink,¹ who points out that the incidence of brucellosis both in domestic animals and in human beings is on the increase. During 1947 more cases were recognized and reported in the country as a whole than in any previous year.

The disease has its reservoir in domestic animals, particularly cattle, hogs, and goats, and three closely related species responsible for human disease, have been identified: *Brucella melitensis*, *Brucella suis*, and *Brucella abortus*. *Brucella melitensis* is found primarily in goats, although it has also been shown to infect cattle. A fact of considerable epidemiologic importance was brought to light recently by the findings in Iowa and Minnesota that *Brucella melitensis* is distributed widely in hogs. The hog is the natural reservoir for *Brucella suis*. However, *suis* has been reported in cattle. *Brucella abortus* occurs primarily in cattle with localization in the udder and in the pregnant uterus of heifers. Infection in man seems to be incidental in the natural history of brucellosis, since the disease is primarily one of domestic animals.

There are two principal routes by which infection occurs in human beings the first by consumption of raw milk and milk products from diseased animals, and the second through contact of the human skin with the tissues, secretions, or excretions of animals with brucellosis. In addition to these common modes of transmission, occasional infection has occurred in persons handling cultures of *Brucella* in the laboratory. The possibility of air-borne infection and the inhalation of viable *Brucella* cannot be dismissed.

Dr. Spink points out that the tissue responses to this infectious agent are rather characteristic, organs belonging to the reticuloendothelial system, the spleen, liver, bone marrow, and lymph nodes, being invaded consistently by *Brucella*. A second feature of importance is the intracellular parasitism of parenchymal cells by these microorganisms. Dr. Spink quotes from studies by Meyer² which were made on the tissues of a patient within three weeks of a fulminating infection: "This selective intracellular parasitism in mesenchymal cells of various organs is doubtless of greatest significance in the pathogenesis of *Brucella* infections." Spink and his associates³ have been interested for some years in the histopathology of tissue reactions in brucellosis, both in experimental animals and in living patients by biopsy techniques. Excellent photomicrographs are included in Spink's article which show the typical granulomatous lesions of various tissues. The outstanding features are proliferation of epithelioid cells with or without giant cells and the presence of lymphocytes, plasma cells, and occasionally eosinophiles.

Of considerable interest is the fact that in three patients in whom repeated cultures of blood showed no growth of organisms, *Brucella* organisms were cultured from the sternal marrow. Another interesting pathologic feature of the disease is the involvement of the liver. As early as 1939 the statement was made⁴ that the most common visceral lesion occurring in brucellosis involves the liver. On the basis of their investigations, Spink and his co-workers are inclined to agree, believing that the hepatic changes should not be considered a complication, but rather a part of the natural history of the disease.

Unusual complications of brucellosis include osseous changes involving the vertebrae, the pelvis, and the long bones. In this connection Spink states that while periarticular distress is not uncommon in brucellosis, the group at Minnesota has not encountered a single case of chronic arthritis resulting from brucellosis. Another complication encountered in their series of cases was sub-acute bacterial endocarditis. Four cases due to *Brucella abortus* were studied and treated. Three of these patients had fatal illness, but the fourth recovered and remained well for over a year following combined treatment with streptomycin and sulfadiazine.

In a section devoted to immune reactions Spink emphasizes the development of hypersensitivity following invasion of the tissues and states that "although it may not be illogical to subject patients with chronic brucellosis to increasing doses of *Brucella* antigens in attempts to 'desensitize' their tissues," their own "efforts in the therapy of brucellosis have been toward eradicating viable *Brucella* from the tissues, thus ridding the body of the source of antigenic material."

Accordingly, the Minnesota group favor the combined use of streptomycin and sulfadiazine in an attempt to eradicate *Brucella* from the body. These agents act in a synergistic fashion and are not merely additive in their effect. Carefully tabulated clinical results with this combined therapy were verified by experimental studies in embryonated hen's eggs infected with brucellosis.⁵ All three species of *Brucella* were investigated.

The clinical observations cover a period of approximately one year. Seventeen patients with brucellosis were treated with streptomycin and sulfonamides, especially sulfadiazine. In fourteen of these patients *Brucella abortus* was isolated. Nine of the cases were designated as the acute form of the illness, being of less than three months' duration. From eight of the nine, *Brucella abortus* was isolated. In general the results were good, and from study of these nine cases, Spink concludes that eight to ten days of combined treatment are required before patients experience definite improvement with return to normal temperature.

Eight patients, in whom the illness was of three months' duration or more, were classified as chronic cases, and from six of these eight patients *Brucella abortus* was isolated. In this group of chronic cases, results of combined therapy were quite similar to those obtained in the acute cases. Slightly larger amounts of streptomycin were administered to the chronically ill patients. On the basis of experience with these seventeen patients, Spink recommends that the total daily dose of streptomycin should not exceed 2 Gm. However, 0.5 Gm. of streptomycin may be given intramuscularly every six hours for two weeks and at the same time 3 to 4 Gm. of sulfadiazine may be administered orally in an initial dose and then 1 Gm. every four hours for a total of three weeks. Spink emphasizes the desirability of hospitalization under close supervision for all patients undergoing therapy, since toxic complications are possible and may be serious.

In a discussion of prevention, Spink points out that "every effort must be made to eradicate the animal reservoir of the disease." He enumerates some of the difficulties involved in this problem, particularly as species of *Brucella* are more widely distributed than was realized formerly. Since no dependable methods of immunization against brucellosis are known for man, control measures are of even greater importance. Danger of contact with infected animals must be emphasized, for brucellosis may become a real occupational hazard for farmers, livestock workers, veterinarians, and abattoir workers.

While it is generally accepted that cow's milk must be pasteurized, there seems to be considerable laxity concerning regulations for the pasteurization of

goat's milk. The increasing awareness that brucellosis is a real medical problem must bring about adequate pasteurization of all milk and milk products, goat included. Implications that the nutritive value of goat's milk is altered by the pasteurization process seem completely unfounded.

Spink poses questions regarding mild, inapparent infections in children and adults. Recognized brucellosis is less frequent in children under 12 years of age than in older age groups, and increased resistance of young children to brucellosis seems to be an established fact. Immune studies carried out by the Minnesota group and elsewhere indicate that the tissues of rural children are invaded by *Brucella*, and that mild infections do occur. Accurate information is not available as to whether one attack or mild infection confers immunity against subsequent attacks. With improved methods of diagnosis and study it seems possible that many more cases in the pediatric age group may be recognized.

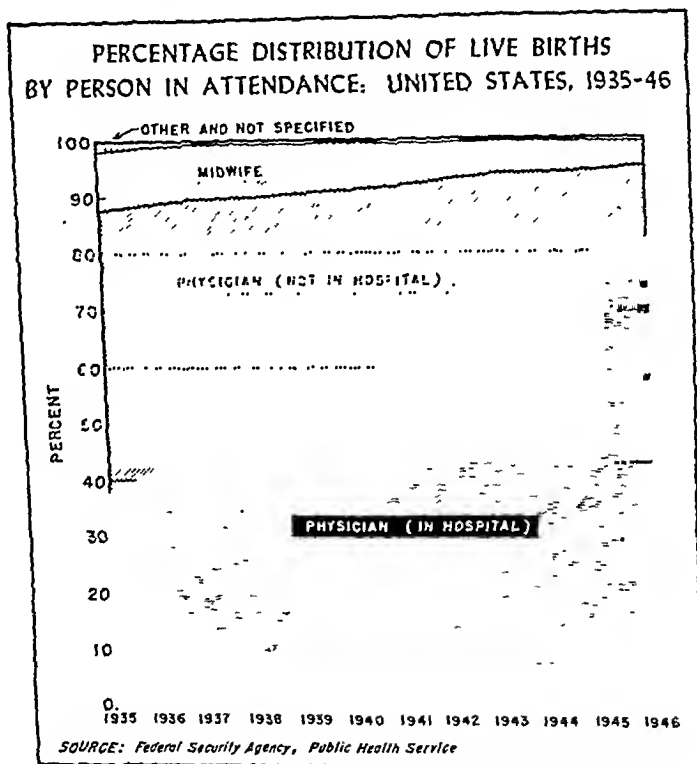
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News and Notes

According to statistics recently released by the National Office of Vital Statistics, a new record was set in 1946 for births delivered in hospitals. Of 3,288,672 live births recorded in 1946, 82.4 per cent occurred in hospitals. Connecticut led with 98.9 per cent, with Washington second with 98.2 per cent. The New England and Pacific Coast states were highest as groups, with the southern states the lowest. The marked increase in hospital births that has taken place since 1935, when such data were first compiled, is shown in the following graph prepared by the Federal Security Agency.



The American Board of Pediatrics will hold examinations at St. Louis, Mo., on Feb. 18, 19, and 20, 1949, and at Baltimore, Md., on April 22, 23, and 24, 1949.

The following were certified by the American Board of Pediatrics at the examination in Seattle, September, 1948:

- Dr. Mason H. Abramson, 90 Birch Street, Redwood City, Calif.
- Dr. Forrest Hood Adams, University of Minnesota Hosps., Minneapolis 14, Minn.
- Dr. Albert T. Aldrich, 153 S. Lasky Drive, Beverly Hills, Calif.
- Dr. Wesley Huntington Anderson, 412 First Security Bank Bldg., Ogden, Utah.
- Dr. Victor J. Birnberg, 6333 Wilshire Blvd., Los Angeles 36, Calif.
- Dr. George Orion Boucher, 529 E. Tenth Street, Long Beach 13, Calif.
- Dr. Mathew D. Burnett, Jr., 5101 Fannin Street, Houston, Texas.

- Dr. Charles Macfie Campbell, Jr., 911 Chapala Street, Santa Barbara, Calif.
Dr. Michael Joseph Campbell, 7943 Exchange Ave., Chicago, Ill.
Dr. Leroy O. Carlson, 717 Baker Bldg., Walla Walla, Wash.
Dr. R. Wendell Coffelt, 628 North Glenoaks, Burbank, Calif.
Dr. John R. Connell, Children's Hospital, Denver, Colo.
Dr. Lewis T. Corum, 241 Lafayette Arcade Bldg., Tampa 6, Fla.
Dr. James Otis Dowrie, 1205—24th St., Sacramento 16, Calif.
Dr. Josephine Lewis Earlywine, 1159 Wilmette Ave., Wilmette, Ill.
Dr. Frank L. Fletcher, 311 W. Idaho, Boise, Idaho.
Dr. Thomas V. Geppert, The Henry Ford Hospital, Detroit, Mich.
Dr. Grace Baker Goebel, 469 Chapman Drive, Corte Madera, Calif.
Dr. Margaret L. Goetsch, 110 W. Broadway, Glendale, Calif.
Dr. Martha Helen Hale, 3403 Hall, Dallas, Texas.
Dr. Herbert Bryan Hutt, 42 W. Midlothian Blvd., Youngstown 7, Ohio.
Dr. Julius M. Kantor, 306 East 12th St., Kansas City, Mo.
Dr. Frank McCarry, 451 Paulsen Medical and Dental Bldg., Spokane, Wash.
Dr. John Patrick McDermott, 515 Cobb Bldg., Seattle, Wash.
Dr. Donald Hemphill McDonald, 1442 North Third, Abilene, Texas.
Dr. John Cunningham Montgomery, Jr., 202 Fine Arts Bldg., Bellingham, Wash.
Dr. Arthur James Moss, 239 North Locust St., Inglewood, Calif.
Dr. Aaron Nisenson, 6230 Wilshire Blvd., Los Angeles, Calif.
Dr. Leon Oettinger, Jr., 4614 Sunset Blvd., Los Angeles, Calif.
Dr. Sam M. Powell, Jr., 1611—5th St., Corpus Christi, Texas.
Dr. A. Martin Puris, 4753 N. Broadway, Chicago, Ill.
Dr. Edgar Moskedal Rector, 4212 N.E. Broadway, Portland 13, Ore.
Dr. Francis H. Redewill, Jr., 124 E. Hadley Street, Whittier, Calif.
Dr. Clark M. Richardson, 829 South Alvarado, Los Angeles 5, Calif.
Dr. Catherine Foss Roberts, 1629 Selby Avenue, Los Angeles 24, Calif.
Dr. Samuel M. Rosenthal, 6333 Wilshire Blvd., Los Angeles 36, Calif.
Dr. Melvin H. Schwartz, 1904 Franklin Street, Oakland, Calif.
Dr. Albert John Sheldon, 1524 N. Broadway, Santa Ana, Calif.
Dr. Ralph Omer Sherberg, 508 Metropolitan Bldg., Denver 2, Colo.
Dr. Frederic E. Simpson, 234 W. Beauregard, San Angelo, Texas.
Dr. Pauline George Stitt, Territorial Dept. of Health, Honolulu, Hawaii.
Dr. Philip Roger Vandeman, General Delivery, Olympia, Wash.
Dr. James Sherman Vedder, Marshfield Clinic, Marshfield, Wis.
Dr. Elsie I. Wisczorowski, 645 Fullerton Pkwy., Chicago 14, Ill.

A postgraduate course in pediatrics was given by the Pediatric Department of the University of Arkansas School of Medicine under the direction of Dr. Wm. A. Reilly, Professor of Pediatrics, Nov. 4 to 6, 1948. Guest speakers were Dr. Waldo E. Nelson, Professor of Pediatrics, Temple University, Philadelphia, Pa., and Dr. Arild E. Hansen, Professor of Pediatrics, University of Texas, Galveston, Texas.

Book Reviews

Ensayo Estadístico sobre Valores Sanguíneos en Lactantes Sanos y Enfermos.* J. J. Murtagh, C. E. Martínez Castro Videla, R. M. Ferro, and H. C. Ferro. Buenos Aires, Argentina, 1947, Librería y Editorial "El Ateneo," pp. 150, 77 tables, and 10 charts; 205 references.

This monograph reports the results of a survey of several hematologic and blood chemical constants in infants under one year of age. The aim was to determine whether or not normal values derived from European and North American populations are applicable to infants in the Argentine.

The hematologic survey is limited to the concentration of hemoglobin, dimensions of the red cells, and the red cell-hemoglobin relations as currently measured or calculated. The blood chemical constituents considered are serum protein; whole blood nonprotein nitrogen and its separate components; whole blood, serum, and erythrocyte chlorides; and the carbon-dioxide combining power of the serum.

The report is divided into three parts: first, a review of the literature relating to the foregoing items; second, the authors' observations on healthy breast-fed and bottle-fed babies; third, their observations on dehydration and other disturbances of the acid-base equilibrium.

The monograph is, in most respects, a model to be imitated. The review of the literature is comprehensive and clear; original data are presented in a compact, understandable manner. The authors are to be congratulated especially on their recognition of the need to analyze the data statistically by the small-numbers method, and on the clarity of their presentation of the theoretical and practical aspects of this technique.

No claim for originality is made; hence, the reader will not be surprised to find only that many firmly established conclusions have been reaffirmed. Nonetheless, original, reliable data are always of value in evaluating the details of homeostasis throughout the world. It is only to be regretted that the investigators did not find it possible to make their blood chemical studies more complete.

D. McC.

Diseases of the Ear, Nose and Throat. William Wallace Morrison, M.D., Professor of Otolaryngology and Attending Otolaryngologist, New York Polyclinic Medical School and Hospital. New York, 1948, Appleton-Century-Crofts, Inc., 772 pages, 359 illustrations. Price \$8.50.

This is a completely new successor to Morrison's previous book under a different title. It is intended as a student textbook and covers the entire field of otolaryngology. The material is well presented, making for easy reading. The illustrations are schematic which aids in the reading matter. Method of examination is explained. Each subject was delved into rather sufficiently and the material has been brought up-to-date. Newer modes of therapy have been included. Operative techniques are discussed enough to enlighten practitioners as to what is done to their patients. It should be a valuable aid to the student and practitioner of medicine as well as an added book on the shelf of practicing otolaryngologists.

CUTLER.

*A Statistical Study of Blood Constituents in Healthy and Sick Infants.

Editor's Column

DEATHS IN CHILDREN DUE TO ACCIDENT

The developments of medical science in the last quarter century have made many striking changes in mortality statistics. Deaths from diarrheal diseases, for example, decreased 91 per cent between 1930 and 1946 in the 1- to 4-year age group, and deaths due to communicable diseases in the 5- to 9-year age group came down 83 per cent. The total reduction in deaths from disease has resulted in accidents becoming the leading cause of death in children. At present about 5,000 children in the 1- to 4-year age group die annually from accidents. Burns cause the largest number of fatal accidents occurring in the home, and motor vehicle accidents are the chief cause outside the home.

It has become almost impossible to pick up a daily newspaper in our metropolitan areas without reading of the death or serious injury of some child due to an accident in the home or on the street. In an effort to reduce accidental deaths in children an educational campaign in accident prevention which should receive the support of every physician is now under way.

While most accidents in young children are due to carelessness and hence are preventable, a most interesting development in connection with the study of the cause of accidents has been the recognition in recent years of what is known as accident-proneness. It has been conclusively shown that certain individuals are especially prone to accidents. Our present knowledge of the subject was reviewed in an interesting article by Bakwin and Bakwin in the June issue of the *JOURNAL* (32: 749, 1948). While the studies so far have been chiefly in the adult field, accident-proneness undoubtedly exists in children. In Rochester, N. Y., a special clinic has been opened to study accident-prone children. It is a new field of medical study with whose developments the physician must keep abreast.

A QUESTION OF SEMANTICS

Attracted by the subject, "Should Sex Education Be Taught in the Public Schools," we tuned in a few weeks ago to a national radio program of supposedly high educational value. It was one of the most stupid debates imaginable. The debaters had quite different things in mind by the term "sex education," and hence the pro and con arguments were quite beyond point and could only leave an uninformed listener in a bewildered state of mind. It was a striking example of the futility of an argument when the question is indefinite and undefined. It reminded us of most of the many discussions over "socialized medicine" in recent years. Whenever we are asked what we feel about "socialized medicine," we ask the questioner to please define exactly what he means by the term. The usual result is that there is very little left for argument, and the conversation turns to one of an amicable discussion of the complex medical problems facing the public and the physician.

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Original Communications

VISUALIZATION OF THE AORTA AND ITS BRANCHES BY RETROARTERIAL DIODRAST INJECTION

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St. Louis, Mo.

RADIOGRAPHIC visualization of the heart and great vessels following intravenous injection of Diodrast is an established procedure.¹⁻¹⁵ In order to obtain diagnostic radiograms, the Diodrast must be injected very rapidly, so that it is present in the heart and great vessels in sufficient concentration to produce a sharply outlined shadow. This technique has been described previously¹⁶ and excellent visualization of the entire right side of the heart and pulmonary arteries has been thus obtained. With dispersion of the Diodrast throughout the pulmonary circulation and its subsequent return to the left auricle, good visualization of the left auricle, left ventricle, and aorta is usually obtained. However, the radiograms are frequently not as good as those of the right side of the heart, and the aorta in particular is often indistinctly outlined.

For these reasons it has been felt that injection of Diodrast directly into the aorta would result in more clearly defined radiograms of the aorta and large arteries. Direct puncture of the abdominal aorta through the paravertebral region has been advocated by dos Santos¹⁷ and later by Wagner.¹⁸ Fariñas¹⁹ developed a technique of catheterizing the femoral artery in the region of Scarpa's triangle and, by manipulation, passing the catheter tip upward to any desired level in the aorta before injecting the opaque material. In an effort to improve these techniques, it was felt that retroarterial injection of opaque material through an artery which originates from the aortic arch would more completely outline the whole length of the aorta. Castellanos²⁰ has used the brachial artery for retrograde injections in diagnosing both coarctation of the aorta and patent ductus arteriosus. Clarence Crafoord²¹ uses essentially the same technique. Instead of making the injection along the whole length of the artery, he prefers to insert a catheter up the artery until the catheter tip reaches the aorta. The injection of opaque material is then made

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through the catheter. Use of the left common carotid artery has been considered because a larger amount of Diodrast can be more rapidly injected into the aorta. Norman Freeman²² has used it successfully in the diagnosis of both coarctation of the aorta and patent ductus arteriosus. In children we consider the left common carotid artery best suited for this procedure, and this vessel has been used in all of our studies.

TECHNIQUE

All patients are given a general ether anesthesia. Preoperative care is the same as that given to any patient who is to receive a general anesthetic. Using sterile surgical precautions, an incision is made in the left supraclavicular area directly over the left common carotid artery. Dissection is carried down to the carotid sheath, which is opened, and the internal jugular vein and vagus nerve are identified. The carotid artery is exposed, and three heavy, braided, silk ligatures are passed around the artery but not tied.

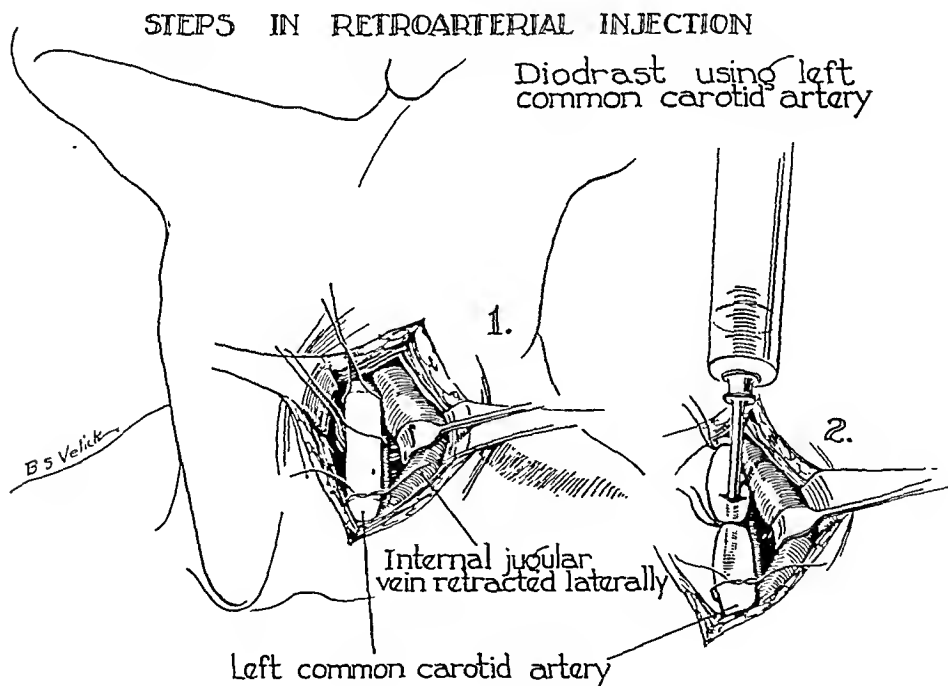


Fig. 1.—Drawing showing steps in retroarterial injection.

The patient is then placed on the tautograph²³ in the right posterior oblique position. In very rapid sequence the upper ligature is tied to prevent cephalad reflux of the dye. The lowermost of the three ligatures is tied loosely at a point approximately one inch below the uppermost ligature. A small incision is made transversely in the vessel wall, and a No. 10 cannula introduced

with the tip extending toward the heart. The third ligature is tied around the vessel just below the opening in the vessel wall and over the shaft of the cannula. This ligature prevents blood leakage. The lowermost tie is loosened, and 30 c.c. to 50 c.c. of 70 per cent Diodrast are injected very rapidly after the tantograph has been started. The lowermost ligature is again tightened and the middle ligature loosened. The cannula is withdrawn and the small opening in the vessel wall sutured with 00000 silk on a nontraumatic needle. The short incision in the neck is repaired in the usual manner. The technical steps are illustrated in Fig. 1.

With this type of injection we have seen much less change in respiration than is seen following intravenous injection of Diodrast. Attempts to utilize the brachial artery have given disappointing results. It is extremely difficult to inject retroarterially over such a long column a sufficient quantity of dye with the rapidity necessary to give sharp delineation of the aorta and its branches.

RESULTS

To date we have studied two types of lesions by this method: patent ductus arteriosus and coarctation of the aorta.

CASE 1.—W. J. F., a 7-year-old girl, was admitted because of a suspected patent ductus arteriosus. On examination a rough "machinery murmur" was audible in the second left interspace, accompanied by a palpable thrill. The blood pressure was 135/72. Fluoroscopy revealed increased pulmonary vascular markings with a heart of normal size. The pulmonary conus was quite prominent.

Retrograde arterial Diodrast studies were performed through the left common carotid artery with radiograms as illustrated in Figs. 2 and 3. Fig. 2 shows Diodrast filling the ascending aorta and aortic arch. In Fig. 3 the whole aorta is well outlined. The pulmonary artery can be seen just anterior to the first part of the descending aorta. The patent ductus can be seen connecting these two structures.

CASE 2.—H. M., a 4-year-old boy, was admitted with a diagnosis of patent ductus arteriosus. On examination all of the classical findings of this condition were present. Retrograde arterial Diodrast studies were performed. In Fig. 4 the descending aorta and a portion of the aortic arch are clearly visualized. Both left and right pulmonary arteries are well filled with opaque material. The patent ductus was subsequently obliterated by operation.

CASE 3.—R. P., a 21-year-old woman, was admitted for study because of a suspected coarctation of the aorta. Preceding studies had revealed slight lowering of systolic blood pressure and a slight decrease in capillary arterial pulsations in the lower extremities. No hypertension was present in the upper extremities.

Retrograde arterial studies were performed. In Fig. 5 the whole aorta is well visualized. A slight constriction of the aorta is seen just distal to the origin of the left subclavian artery.

CASE 4.—G. B., a 14-year-old boy, was admitted because of increasing dyspnea on exertion and easy fatigability during the past year. The important features noted on examination were as follows: A loud systolic murmur accompanied by a systolic thrill was present over the base of the heart with maximum intensity over the aortic area; pulsations of the femoral and dorsalis pedis arteries were weak. Blood pressure studies were: Right arm 127/96, left arm 130/94, right leg 120/84, left leg 124/80. Special studies revealed a decreased blood flow and a decrease in arterial pulsation in the lower extremities as compared to the upper extremities.

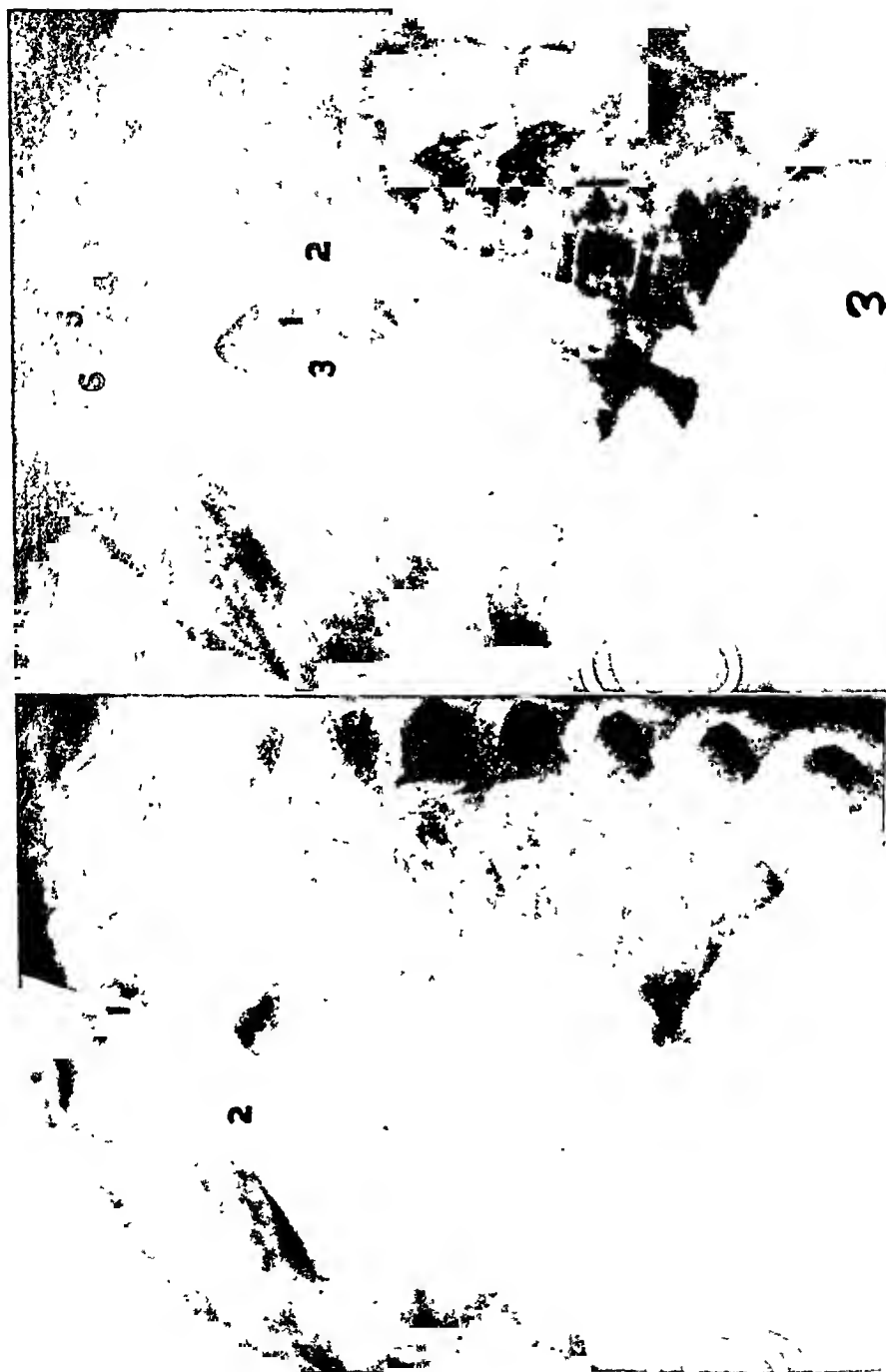


Fig. 2.

Fig. 2.—Left anterior oblique radiogram. 1, Left common carotid artery. 2, Ascending aorta.

Fig. 3.

Fig. 3.—Left anterior oblique radiogram. 1, Patent ductus arteriosus. 2, Descending aorta. 3, Pulmonary artery. 4, Left subclavian artery. 5, Left common carotid artery. 6, Innominate artery.



Fig. 4.

Fig. 4.—Left anterior oblique radiogram. 1, Left common carotid artery. 2, Descending aorta. 3, Left pulmonary artery. 4, Right pulmonary artery.

Fig. 5.

Fig. 5.—Left anterior oblique radiogram. 1, Very slight indentation in anterior wall of descending aorta.



Fig 6

Fig 6—Left anterior oblique radiogram
Fig 7—Left anterior oblique radiogram

Fig 7

1, Left ventricle 2, Ascending aorta 3, Point of constriction of descending aorta
1, Left common carotid artery 2, Left subclavian artery 3, Point of constriction of descending aorta

An angiocardiogram was done with 70 per cent Diodrast injected intravenously. Fig. 6 shows one of the last of ten radiograms taken at one second intervals following the injection. The left auricle, left ventricle, and ascending aorta are well visualized. There appears to be a constriction of the aorta in the midportion of the aortic arch. Just distal to this is a second point of constriction and angulation.

A retrograde arterial study was performed two days later. In Fig. 7 the aortic arch appears well filled with Diodrast. There is slight narrowing of the aorta between the left common carotid artery and the left subclavian artery. Just distal to the left subclavian artery is a sharp constriction. Comparison of Figs. 6 and 7 demonstrates the superiority of the radiograms made with the retroarterial procedure.

Although the constricted area is very narrow in length, it was felt this patient should not have a corrective operation because of the absence of hypertension and because the coarctation was not of sufficient severity to interfere seriously with the flow of blood through the aorta.

CASE 5.—N. P., an 8½-year old white girl, was admitted with an acute recurrence of rheumatic fever. The most important physical findings were as follows: There were marked suprasternal and carotid pulsations; the heart was enlarged to the left with a systolic and diastolic murmur present over the apical region and also over the second and third right and left interspaces. Capillary pulsations and a Corrigan pulse were noted. A loud, systolic murmur was present over the scapular region. Blood pressure readings were as follows: right arm 180/110, left arm 110/70, right leg and left leg not obtainable. Special studies revealed a decreased blood flow and decreased arterial pulsations in both lower extremities.

An intravenous angiocardiogram was done. Only fair visualization of the ascending aorta was obtained with no clear definition of the constricted segment. A retrograde arterial study was performed as illustrated in Figs. 8 to 11. In Fig. 8 the ascending aorta and left common artery are seen. In Fig. 9 a sharp constriction is seen at the beginning of the descending aorta. The innominate, right subclavian, and internal mammary arteries are well visualized. The coronary artery may be seen just posterior to the first part of the ascending aorta. Fig. 10 reveals the same structures as were just described and in addition, shows some of the extensive collateral circulation. The left subclavian artery arises from the distal part of the constricted segment opposite. In Fig. 11 the aortic arch is seen empty of opaque material, although the descending aorta is still filled.

The clinical diagnoses in this patient were: (1) coarctation of the aorta, (2) mitral stenosis and insufficiency, (3) aortic insufficiency.

CASE 6.—W. W., a 15 year old boy, was hospitalized for investigation of hypertension. His subjective complaints were severe headaches and blurring of vision following exercise. Physical examination revealed a systolic and diastolic murmur over the base of the heart. The blood pressure was: right arm 165/105, left arm 160/100, right leg 100/90, left leg 95/90. Pulsations of the abdominal aorta and femoral arteries were very feeble. Notching of the ribs was demonstrated by roentgenography.

Retroarterial injection of Diodrast was carried out, using the left common carotid artery. Serial roentgenograms taken following the injection are seen in Figs. 12 to 15. Fig. 12 reveals early visualization of the aortic arch, innominate artery, and left subclavian artery. In Fig. 13 the coarcted segment of aorta can be seen just distal to the origin of the left subclavian artery. A network of dilated deep arteries of the neck can be seen arising from the left subclavian artery and anastomosing with a dilated intercostal artery arising from the aorta distal to the coarctation. Dilated internal mammary arteries and the left subscapular artery are clearly seen. In Fig. 14 the aortic arch is no longer seen. The site of coarctation and the descending aorta are still visualized. Note the extensive collateral circulation. Fig. 15 demonstrates the dilated intercostal arteries.

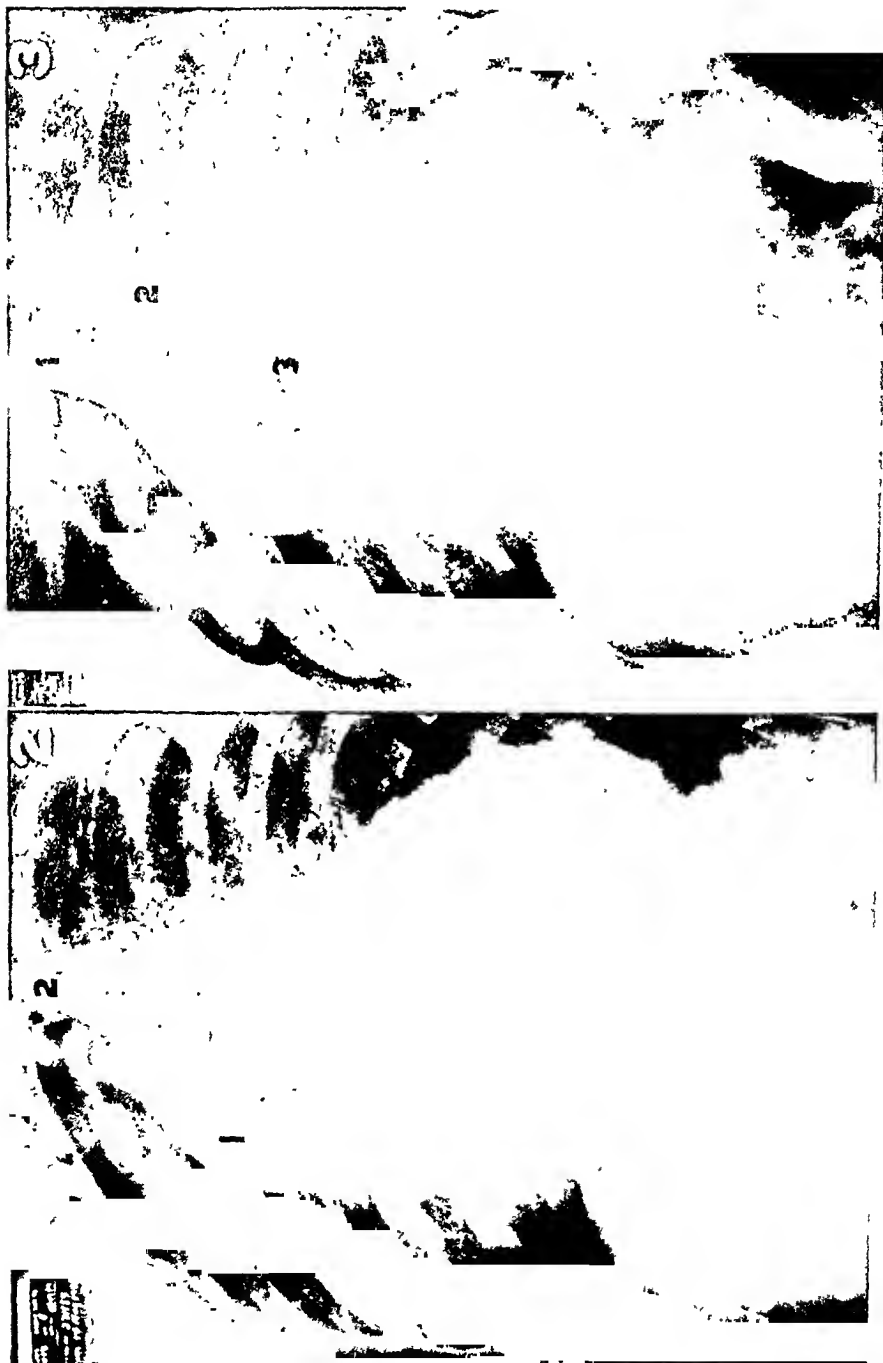


Fig. 8.

Fig. 8.—Left anterior oblique radiogram. 1, Ascending aorta. 2, Left common carotid artery.

Fig. 9.

Fig. 9.—Left anterior oblique radiogram. 1, Innominate artery. 2, Constricted segment of aorta. 3, Coronary artery.

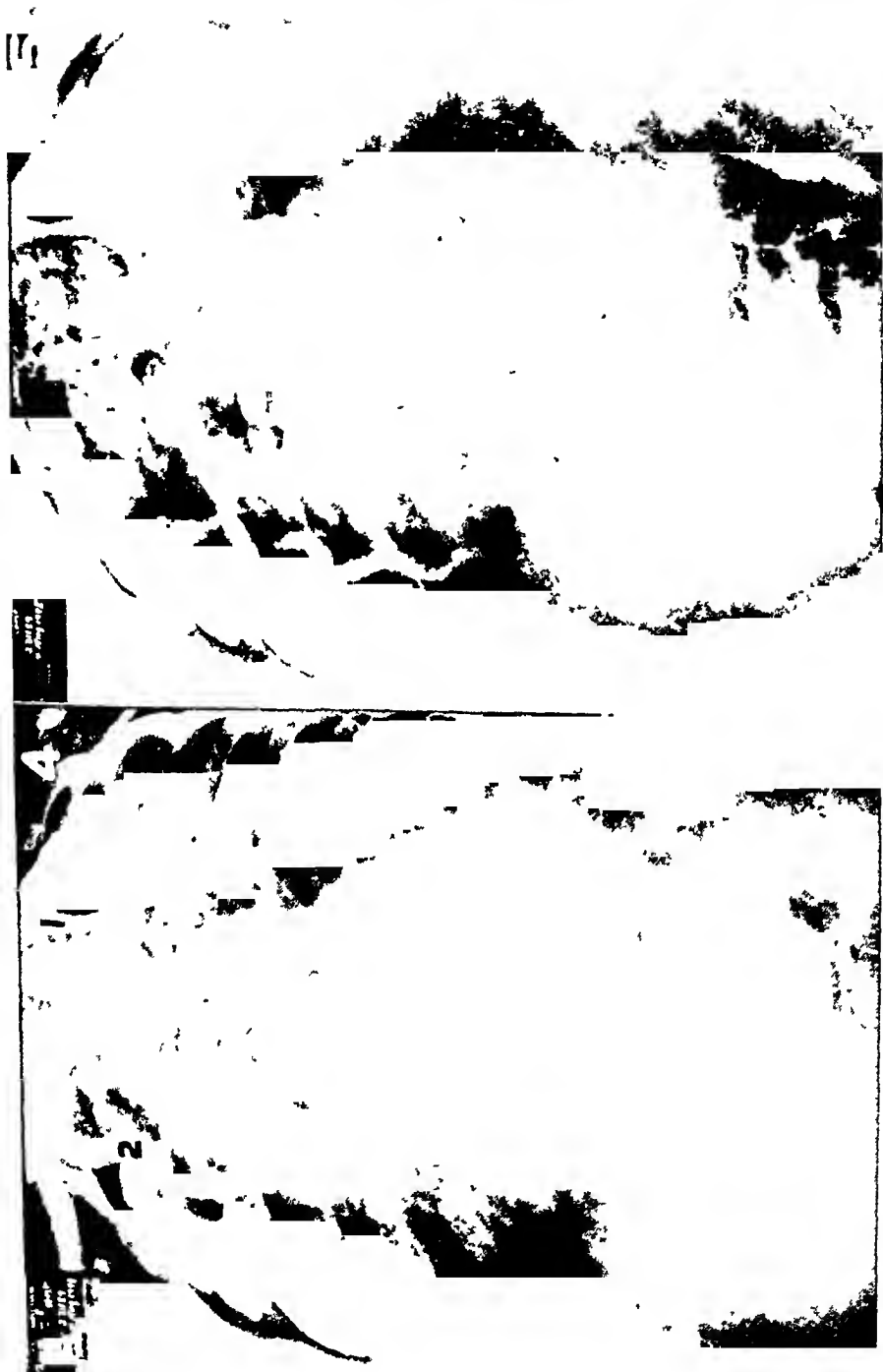


Fig. 10.—Left anterior oblique radiogram 1, Left subclavian artery. 2, Internal mammary artery.
 Fig. 11.—Left anterior oblique radiogram

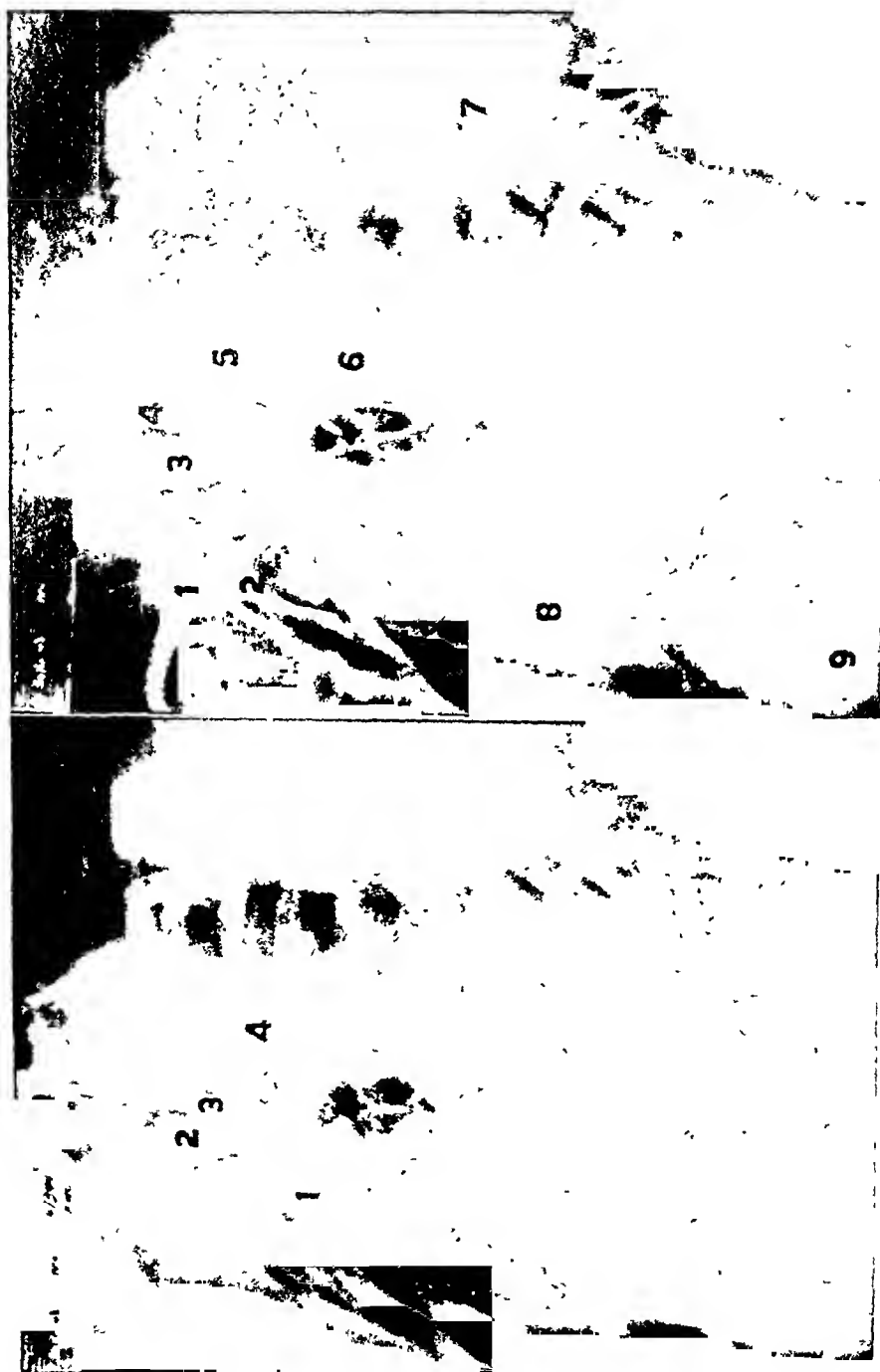


Fig. 12.

Fig. 13.

artery. Fig. 12.—Left anterior oblique radiogram. 1, Ascending aorta. 2, Innominate artery. 3, Left common carotid. 4, Left subclavian artery.

Fig. 13.—Left anterior oblique radiogram. 1, Right subclavian artery. 2, Right internal-mammary artery. 3, Right innominate artery. 4, Left common carotid. 5, Left subclavian artery. 6, Point of coarctation of the aorta. 7, Left subscapular artery. 8, Left internal mammary artery. 9, Epigastric artery.

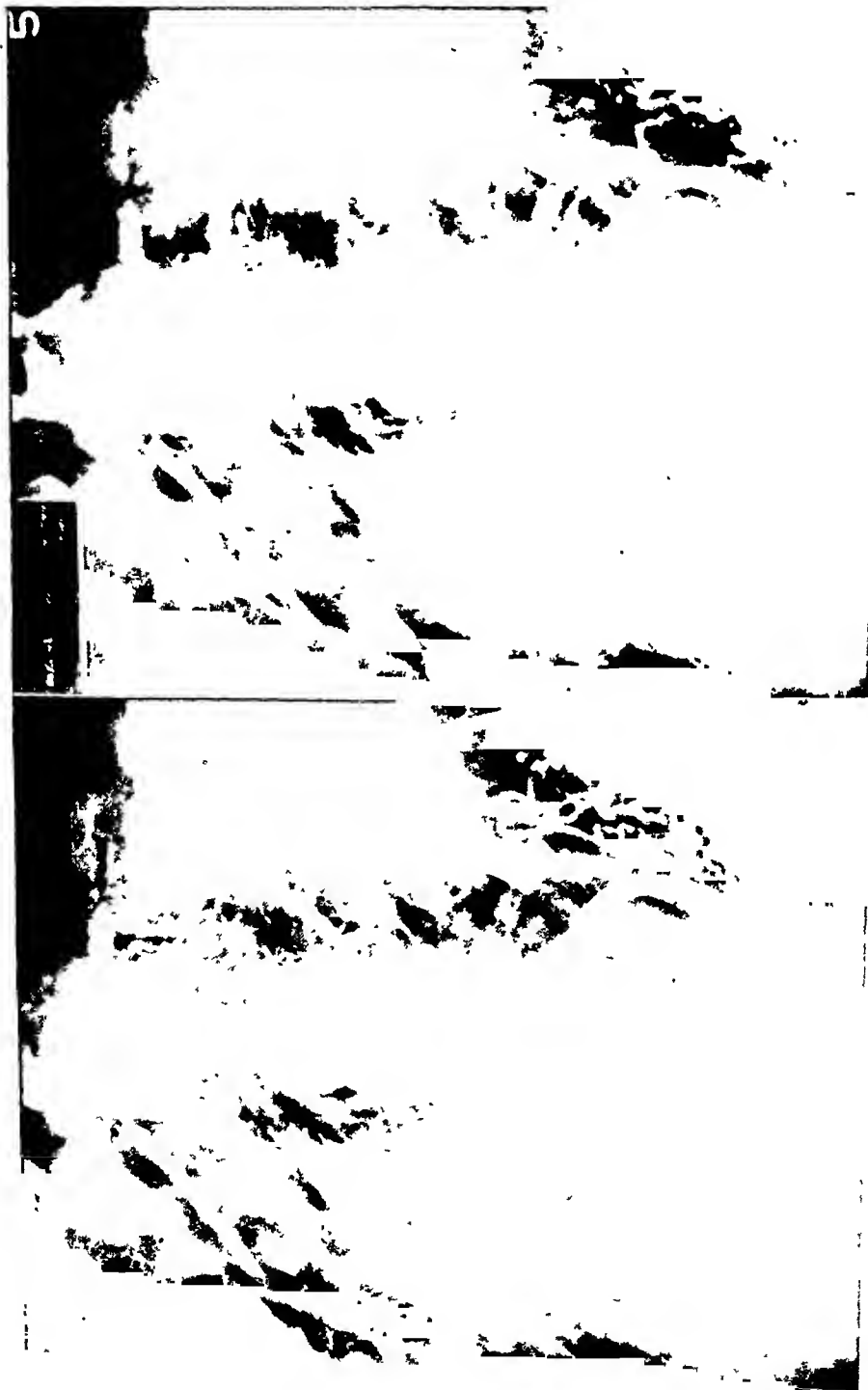


Fig. 14.—Left anterior oblique radiogram.

Fig. 15.—Left anterior oblique radiogram.

DISCUSSION

The technique of retroarterial injection of radiopaque material for visualization of the aorta and its branches is a safe and valuable complement to intravenous injection for visualization of the heart and pulmonary circulation. This procedure may be employed to establish the diagnosis of an arteriovenous shunt between the aorta and pulmonary circulation. In some cases a patent ductus arteriosus may actually be visualized. When the ductus is not seen, filling of the pulmonary arteries simultaneously with filling of the aorta is proof that a direct shunt exists.

When surgery is contemplated in patients with coarctation of the aorta, the point of constriction may be definitely localized in this manner. Unless a complete aortic atresia is present, it is also possible to determine preoperatively whether or not the constricted segment is sufficiently localized to allow surgical resection and anastomosis.

Other congenital anomalies of the aorta such as aortic "ring," or aberrant vessels with tracheal or esophageal compression can, we are certain, be clearly demonstrated by this method. So far we have not had an opportunity to visualize a case of this type. We have definitely been able to rule out aneurysms of the aorta in this way.

It is fortunate that the large field of applicability of this procedure is in the younger age group. It should be pointed out that utilization of the carotid, even though the procedure is a temporary one, is fraught with some hazard in adults. One can, we believe, use the carotid artery very safely in children. In the group of eight patients which have been studied, we have had no complications and no manifestations to suggest that there had been interference, even temporarily, with adequate blood supply to the brain.

CONCLUSIONS

A method of retroarterial Diodrast injection for the visualization of anomalies or disease of the aorta and its immediate branches is presented. Utilization of the left common carotid artery has proved satisfactory. This method provides a safe, dependable, and effective means of diagnosing questionable cases of patent ductus arteriosus, coarctation of the aorta, and aortic arch anomalies, and is useful in proving or disproving selected cases of aneurysms.

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ELECTROPHORETIC STUDIES OF PLASMA AND URINARY PROTEINS IN CHILDREN WITH LIPOID NEPHROSIS

J. I. ROUTH, PH.D., E. L. KNAPP, PH.D., AND C. K. KOBAYASHI, M.D.
IOWA CITY, IOWA

INTRODUCTION

AS a part of an extensive series of clinical and chemical studies of lipoid nephrosis in children, electrophoretic analysis of the plasma and urine appeared to offer a source of valuable data concerning the distribution of the protein fractions in this disease. In recent years, electrophoresis has been applied to a study of the plasma proteins in various diseases.¹ Several cases of nephrosis have been discussed in these studies, but none of the investigators has been primarily concerned with nephrosis in children. In 1939, Longsworth and MacInnes² observed abnormal electrophoretic patterns of the plasma and urine of two nephrotic patients, whose ages were not given. The plasma and urinary proteins of several patients with nephrosis, three of whom were children, have been studied electrophoretically by Luetseher.^{3, 4, 5} Also Thorn and associates⁶ have made similar studies of seven adults in the nephrotic stage of chronic nephritis during treatment with concentrated serum albumin. Studies of two children with lipoid nephrosis were included in a series of investigations by Janeway and his co-workers.

The present study concerns an electrophoretic analysis of the plasma and urine of children with lipoid nephrosis. For five children the studies were made before, during and after treatment with concentrated, salt-poor human serum albumin.*

PROCEDURE

Plasma or urine samples were diluted with buffer to a protein concentration of 1.5 to 2.0 per cent and dialyzed at 2 to 6° C. for three days with daily change of buffer.

The buffer solution was 0.1 normal sodium diethyl barbiturate with a pH of 8.6 and an ionic strength of 0.1. Electrophoresis of the dialyzed plasma was performed at 0.8° C. in the apparatus described by Tiselius⁷ using the long center section cell. The Schlieren scanning device of Longsworth⁸ was used to obtain Schlieren diagrams of the plasma proteins. Tracings of the diagrams were prepared by projecting the photographic negatives magnified two and one-half times on a glass screen. Patterns from the descending boundaries were then analyzed according to the following methods. The components were

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*The serum albumin used in this study was processed by the American National Red Cross from blood which it collected from voluntary donors.

This is one of a series of investigations on serum albumin being carried out with material supplied by the American National Red Cross. As soon as sufficient data become available to justify final conclusions concerning its therapeutic value, a full report to the medical profession on the use of serum albumin in medical practice will be published by the Committee on Blood and Blood Derivatives of the Advisory Board on Health Services of the American National Red Cross.

resolved by the method of Pedersen¹⁰ and the area of each component determined by planimetric measurement. The percentage composition of the plasma proteins was calculated by comparing the area of each component with the total area of the tracing. Electrophoretic mobilities of the various components were calculated from the distance the component moved during electrophoresis, the current, time, the cross-section area of the cell, and the conductivity of the protein solution.

Some of the plasma samples contained suspended fat globules which scattered the light and interfered with photography of the Schlieren diagrams. Centrifugation in the cold at 5,500 r.p.m. was used in an attempt to clarify several of these samples. Photographic compensation involving the use of light filters and increased illumination was also employed to overcome this interference. If these methods were unsuccessful, the data from these samples were discarded.

It was realized that the so-called β -globulin disturbance present in the majority of the plasma patterns was caused by lipoproteins in clear solution in the plasma which migrate at approximately the same rate as the α_2 - and β -globulins. Since extraction of the plasma with fat solvents removed an unknown quantity of this characteristic lipid material as well as the suspended fat,² this method was not employed to clarify the plasma samples containing fat.

DISTRIBUTION OF PROTEINS IN NEPHROTIC SERA

The data for the percentage composition of the plasma proteins and the total protein concentration in grams per 100 ml. plasma are shown in Table I. For purposes of comparison, we have included average values for percentage composition of the plasma of thirteen normal children.¹¹ Total protein concentration was determined by a colorimetric micro-Kjeldahl method.

The changes in the percentage composition of the plasma proteins in nephrosis were very striking. Abnormal variations in albumin, α_1 -, α_2 -, and β -globulins occurred in all stages of the disease. As noted by others previously^{1, 2, 3, 6} the albumin concentration was markedly reduced, while the α - and β -globulins were increased. With prolongation of the disease, variations from the normal pattern became more marked. The concentration of albumin was further reduced and in most instances the α_2 - and β -globulin content increased as the albumin decreased. See, for example, in Table I the figures for G. S., compared with those for S. S., before and after recovery from nephrosis. Patient S. S. was ill only a short time, developed measles, had only moderate edema, and recovered promptly. The electrophoretic pattern of her plasma proteins showed a decrease in albumin, an increase in β -globulin, only a slight elevation in α_2 -globulin, and normal α_1 -globulin concentrations. Patient G. S. had been chronically ill for eleven months with marked ascites requiring repeated paracenteses. The albumin concentration in his plasma was greatly reduced, the β - and α_2 -globulin concentrations greatly elevated, and α_1 -globulin concentration normal or increased.

In some cases, the α_1 -globulin concentration also increased concomitantly with the α_2 - and β -globulins, e.g., H. A., on March 3, 1947. In others, e.g., H. A.,

TABLE I. ELECTROPHORETIC ANALYSES OF PLASMA PROTEINS OF CHILDREN WITH NEPHROSIS

SUB- JECT	SEX AND AGE	DATE	ALBUMIN THERAPY	TOTAL PROTEIN (GM./100 ML.)	PERCENTAGE COMPOSITION					
					ALB. A	GLOBULINS				
						α_1	α_2	β	δ	γ
<i>I. Severe Edema and Ascites Requiring Frequent Paracenteses for Several Months</i>										
G. S.	M 3	7/19/46	None	3.6	2.5	3.5	45.0	33.8	12.5	2.7
		7/27/47	5 c.c. γ -globulin i.m. 7/19 to 7/26	4.4	6.2	3.1	26.7	44.2	15.6	4.2
		10/29/46	None	3.8	7.8	6.5	30.4	32.6	7.4	15.2
D. M.	M 3	11/19/46	None	6.0	1.4	21.8	25.8	28.0	9.6	13.4
		6/21/46	None	4.5	5.3	3.2	47.9	20.7	19.7	3.2
		6/22/46	25 Gm.	4.9	4.7	9.9	56.7	16.4	11.7	0.6
		6/23/46	25 Gm.	4.5	9.8	13.6	48.8	17.5	9.8	0.5
		6/24/46	25 Gm.	4.5	9.9	9.9	53.2	17.6	6.4	3.0
		6/25/46	None	4.4	12.1	19.1	35.0	16.1	13.4	4.3
J. W.	F 3	11/19/46	None	4.6	13.3	27.5	34.4	7.1	14.4	3.3
		6/17/46	None	5.5	6.8	6.1	28.0	39.4	17.4	2.3
		6/18/46	After 20 Gm.	5.2	8.1	11.0	46.2	17.6	13.8	3.3
		11/19/46	None	5.0	12.2	29.4	31.0	10.0	15.0	2.4
J. O.	F 3	4/24/47	25 Gm. daily	4.8	13.2	13.2	35.1	21.5	13.2	3.7
		5/15/47	4/24 to 6/1	5.9	47.3	3.3	25.9	14.9	6.4	2.2
		7/24/47	25 Gm. daily	4.5	9.3	20.4	38.7	13.7	14.7	3.2
		9/3/47	7/25 to 9/15	6.3	30.1	18.5	26.8	6.5	15.3	2.8
		10/1/47	None	4.3	4.4	28.1	34.0	10.7	15.9	6.9
T. V.	M 2	10/22/47	None	5.1	9.3	5.0	61.6	10.6	11.1	2.4
H. A.	M 7	10/27/47	None	4.5	12.2	26.0	41.1	10.2	9.8	0.7
		10/28/46	None	4.2	16.7	3.6	28.2	30.7	7.9	12.9
		3/3/47	None	4.9	5.8	15.1	35.0	30.2	9.8	4.1
		3/13/47	25 Gm. daily	4.4	17.4	4.6	38.9	22.2	10.5	6.4
		4/15/47	3/3 to 5/1	5.1	16.2	5.8	49.2	12.1	11.6	5.1
		5/2/47		4.9	21.7	4.1	38.2	21.6	10.6	3.9
		5/15/47	25 Gm. daily	4.0	20.5	26.0	33.8	7.2	9.8	2.7
		6/19/47	5/19 to 6/17	4.5	18.3	3.8	38.0	22.7	11.2	6.0
7/29/47	None	5.1	16.8	31.5	31.1	7.2	8.7	4.7		
<i>II. Moderate Edema, Ascites not Severe</i>										
R. H.	M 4	11/19/46	None	4.8	22.3	26.4	32.2	6.2	6.1	6.8
C. T.	F 8	5/9/47	25 Gm. daily	5.4	19.8	23.3	30.0	8.5	15.8	2.6
		5/27/47	5/19 to 6/3	5.2	38.5	4.6	21.6	22.7	8.0	4.6
		6/19/47	None	4.3	16.4	9.2	34.8	20.8	14.5	4.3
<i>III. Early Stage of Disease with Minimum Edema</i>										
R. D.	M 3	11/19/46	None	5.6	21.7	2.4	18.3	28.2	9.0	10.4
S. S.	F 4	7/10/46	None	8.2	32.9	4.3	13.8	29.8	10.8	8.4
		7/13/46	After 25 Gm.	6.9	39.1	2.6	13.3	31.1	7.1	6.8
<i>IV. Completely Recovered</i>										
S. S.	F 4	6/24/47	None (recovered)	7.9	60.6	6.5	8.9	12.6	4.1	7.3
J. K.	M 3	4/29/47	None (recovered)	8.0	57.3	8.0	11.3	11.3	5.0	7.1
Average values for thirteen normal children (3-8 years)				7.5	57.7	6.3	10.6	10.3	5.2	9.7

on May 15, 1947, and D. M., on Nov. 19, 1946, α_1 -globulin appeared to be increased at the expense of β -globulin.

The fibrinogen fraction also exhibited a fairly regular increase as the albumin decreased. The γ -globulin content of the plasma of the majority of the nephrotic children was definitely lower than that of the plasma of normal children of the same age.

Schlieren diagrams of representative plasma samples are illustrated in Figs. 1 to 4. Fig. 1 shows the electrophoretic pattern from the plasma of a normal child. Fig. 2 shows the pattern obtained by electrophoresis of the

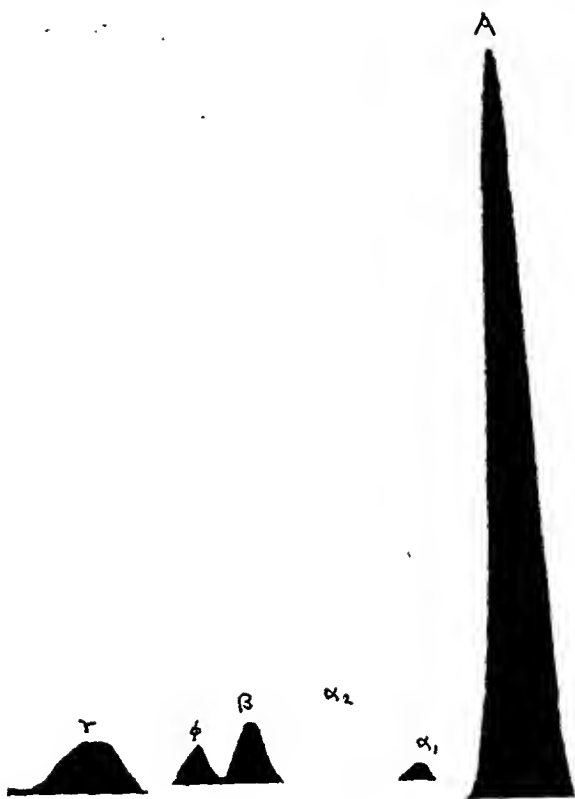


Fig. 1.—Plasma from a normal 4-year-old boy.

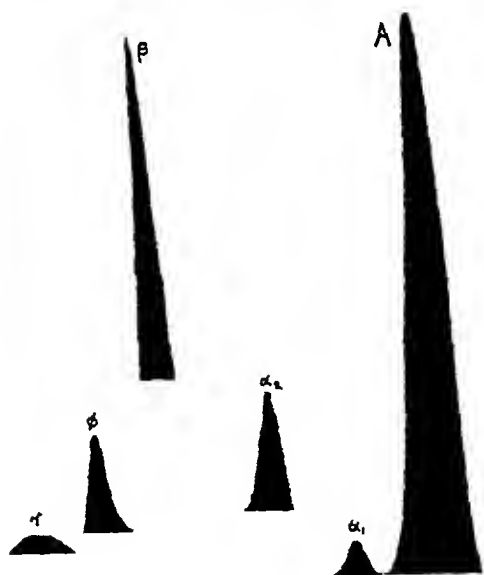


Fig. 2.—Plasma from a 4-year-old girl, S. S., with nephrosis of two months' duration. Edema had been minimal for the previous month.

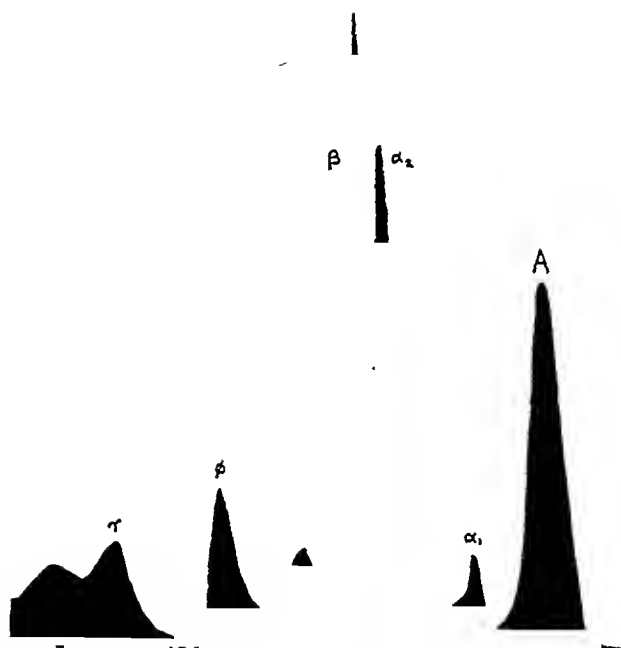


Fig. 3.—Plasma from R. D., a 3-year-old boy with nephrosis for the previous nine months. Edema was not marked at the time the blood sample was analyzed.

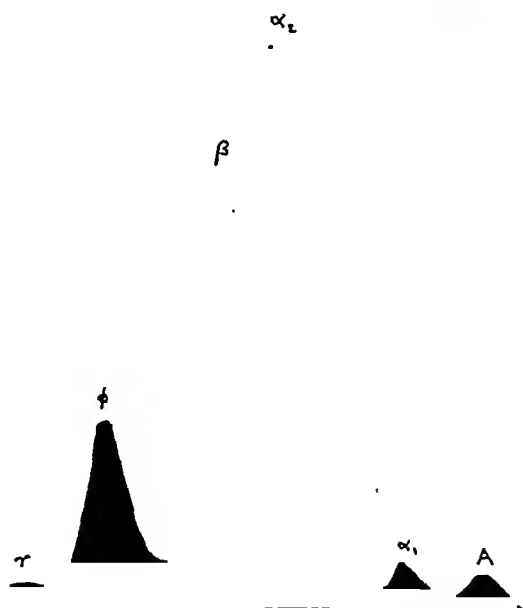


Fig. 4.—Plasma from G. S., a 2-year-old boy with nephrosis for eleven months. The child had severe edema and ascites requiring frequent paracenteses and was very ill at the time of the plasma analysis.

plasma of a nephrotic child early in the course of the disease (S. S., July 26, 1946). The albumin content has decreased to 39 per cent and the β -globulin content is abnormally high. A further decrease in the albumin and an increase in the β -globulin disturbance may occur in later stages of this chronic disease. For example, the pattern for R. D., Nov. 25, 1946 (Fig. 3), who had been ill for nine months, shows a decrease in albumin to 22 per cent and a very pronounced α_2 - and β -globulin disturbance. Even greater decreases in albumin, to as little as 2.5 per cent of the total proteins with corresponding increases in globulin, have been noted when the child has been seriously ill for many months with pronounced edema and marked undernutrition. (See Fig. 4, G. S., July 29, 1946.)

In analyzing the tracings from Schlieren diagrams which are as abnormal as those obtained from plasma of nephrotic children, the mobility measurements are very important. These measurements were made for every pattern that was analyzed but the data are not included in the tables reported here. The distance a component has moved during electrophoresis is an essential value in establishing the location of the area on the pattern caused by a specific protein component. The mobility measurements of the plasma proteins for any one patient show normal variation from one determination to the next. When the values for the plasma proteins in nephrosis are compared with those from normal children of the same age, there appears to be a slight decrease in mobility of each protein component, but this decrease is of questionable significance.

Data from the electrophoretic analyses of urinary and body fluid proteins from nephrotic children are shown in Table II. The electrophoretic patterns of most of the urine samples were similar to that shown in Fig. 5. The protein

TABLE II. ELECTROPHORETIC ANALYSES OF URINE AND BODY FLUIDS OF CHILDREN WITH NEPHROSIS

SUBJECT	SEX AND AGE	DATE	ALBUMIN THERAPY	TOTAL PROTEIN	PERCENTAGE COMPOSITION					
					ALB. A	GLOBULINS				
						α_1	α_2	β	δ	γ
Urine (Gm./day)										
H. A.	M 7	3/1/47	None	12.8	43.9	19.5	10.2	9.3		17.1
		4/3/47	25 Gm. daily	29.0	79.9	11.8		4.5		3.8
D. M.	M 3	4/30/47	3/3 to 5/1	34.8	87.0	9.2		3.8		
		6/21/46	None	8.4	72.1	21.0		6.9		
		6/22/46	25 Gm.	17.9	88.2	9.1		2.8		
		6/23/46	25 Gm.	18.5	89.0	7.6		3.4		
		6/24/46	25 Gm.	11.3	92.3	5.2		2.6		
S. S.	F 4	6/25/46	None	4.1	88.9	8.5		2.7		
		7/10/46	None	1.1	89.9	6.9		3.3		
		7/11/46	After 25 Gm.	3.9	69.7	7.1	8.9	14.3		
		7/13/46	None	1.3	84.6	3.8				
J. W.	F 3	6/18/46	After 20 Gm.	11.7	71.0	17.2		8.6		11.5
Body Fluids (Gm./100 ml.)										
H. A. (ascitic fluid)	M 7	3/2/47	None	0.10	24.3	14.2	27.0	8.9	14.2	11.3
		10/28/47	None	0.59	16.2	11.9	34.3	8.7	11.4	17.6
		3/2/47	None	0.19	15.7	7.3	42.6	6.3	15.3	12.8
T. V. (ascitic fluid)	M 2	8/14/47	25 Gm. daily for 21 days	0.26	54.1	7.6	27.5	5.4	3.0	2.4

components present in these samples were identified by calculation of their mobilities. The two globulin components common to every sample were α_1 - and β -globulin. In a few samples α_2 - or γ -globulins were present, and in one case (H. A., March 4, 1947) all of the components of plasma, except fibrinogen, were present.

A

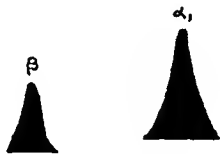


Fig. 5.—Urine from D. M., a 3-year-old boy, severely ill with nephrosis for eleven months. The child had marked edema and ascites requiring frequent paracenteses at the time of the study.

The ascitic and pleural fluids from H. A. and T. V. were very low in protein content. Before analysis they were concentrated by fanning them in Visking casings. Electrophoretic analysis of the fluids from H. A. gave values for protein fractions that were similar to those obtained from his plasma, although in every case the fluid contained a lower percentage of β -globulin and a somewhat higher percentage of albumin than the plasma. The ascitic fluid from T. V. contained a much higher percentage of albumin than the plasma, although these samples were drawn at such different dates that they are not strictly comparable. The plasma sample that was collected the same day the fluid was drawn was so lipemic that the pattern could not be analyzed.

EFFECTS OF ADMINISTRATION OF CONCENTRATED HUMAN SERUM ALBUMIN

Early in this study it was believed that the more accurate definition of the plasma proteins by electrophoretic analysis might be useful in following the effects of therapy. Concentrated human serum albumin was injected intravenously in several children in an attempt to increase the albumin content of

their plasma to a sufficiently high level to overcome the edema and improve their clinical condition. Usually 25 Gm. of albumin were injected daily. At first the effects of one day's administration (See Table I, J. W., June 18, 1946, and S. S.) and three consecutive daily injections (D. M.) were studied. Even though the percentage of albumin in D. M.'s plasma more than doubled during the treatment (5.3 to 12.1 per cent) no clinical improvement was observed. These results are similar to those observed by Luetscher,⁶ who studied the effects of a single dose of albumin in nephrotic patients. Other children were then given daily injections for as many as sixty days or a total of 1,500 Gm. albumin. The response to these larger doses varied with the child. No striking changes in plasma albumin were noted in H. A., although he received a total of 2,250 Gm. of albumin in two periods of treatment. After an initial increase from 5.8 to 17.4 per cent, the albumin content did not rise above 22 per cent. Three other children (J. W., J. O., and C. T.) showed a better response and marked increase in plasma albumin percentage after intravenous albumin therapy for periods varying from two to five weeks (See Table I). These observations are in accord with those of Thorn and associates⁶ and Janeway and associates⁷ who found that large amounts of albumin had to be administered before any improvement was observed in children or in adults with nephrosis. They also found that when the albumin level in the plasma was temporarily raised by an injection of concentrated albumin, there was a corresponding increase in protein excretion. Our findings on the amount of protein excreted in the urine after albumin injections agree with their observations.

DISCUSSION

The results of the present study have confirmed the well-known observation of a very low concentration of plasma albumin in lipoid nephrosis. Also confirmed is the increase in the concentrations of plasma globulin above normal limits as reported by Gottfried and associates,¹² Bloek and associates¹³ and others. The increase in globulin concentration is both relative as shown by the increase in percentage distribution of the various globulin fractions and also absolute. Calculation of the grams of total globulin for eight of the nephrotic children studied from values for total protein obtained by chemical analysis gives values of 3.3 to 4.1 Gm. globulin per 100 ml. plasma. These values are much higher than the accepted normal range of 1.2 to 2.5 Gm. per 100 ml. The α_2 - and β -globulin fractions seem to show the greatest increase but α_1 -globulin may also be increased. Frequently if α_1 is high, β is not elevated markedly above normal. The reason for this apparent reciprocal relationship is not understood.

Possible explanations for the changes in globulin fractions observed in lipoid nephrosis can be postulated. As the albumin content of the plasma decreases either from decreased production, increased excretion, or a combination of these causes, the globulin components account for an increasingly higher percentage of the total plasma proteins. Globulins, having larger molecules, are not excreted so rapidly nor to so great an extent as albumin, therefore

favoring their relative increase in the plasma. The fact that α_2 - and β - and, many times, α_1 -globulins are increased disproportionately over fibrinogen and γ -globulin may be explained by the increase in the lipoprotein fraction in the plasma of nephrotic children. The lipoprotein fraction is usually associated with α_2 - and β -globulins and would be reflected in the area of these components when a plasma containing the lipid material was subjected to electrophoretic analysis. Since antibodies are known to be included in the γ -globulin fractions, the lower than normal concentration of γ -globulin in these nephrotic patients may explain the well-recognized susceptibility of these children to intercurrent infections.

Administration of concentrated salt-poor human serum albumin to children with nephrosis produced no striking changes in plasma protein distribution. Short periods of albumin administration of one to three days produced no change in the concentration of plasma albumin, confirming the findings of others.^{5, 6, 7} Daily administration of 25 Gm. of albumin for periods of two to six weeks or longer usually brought about a moderate increase in the percentage of albumin, a decrease in the percentage of α_1 -globulin, and often a decrease in β -globulin. In no case did concentration of plasma albumin, expressed as percentage of total protein or as grams per 100 ml., reach normal values. The administration of concentrated serum albumin to these children with lipid nephrosis proved to be an effective diuretic but the marked diuresis, disappearance of edema, and resultant loss of weight were soon nullified by reaccumulation of edema fluid after termination of daily albumin administration. The clinical significance of these findings will be discussed in detail, together with our conclusions as to therapeutic value of salt-poor albumin in lipid nephrosis, in a later paper.¹⁴

SUMMARY

1. Electrophoretic analyses have been made of plasma samples from eleven children with lipid nephrosis. Distribution of the plasma protein fractions was determined in various stages of the disease and after intravenous administration of concentrated human serum albumin for periods of one to sixty days.

2. In general, the following changes from the normal percentage distribution of plasma proteins were noted in nephrosis: (a) a decrease in albumin, varying with the severity and duration of the disease; (b) an increase in α_2 - and β -globulins and fibrinogen; (c) often an increase in α_1 -globulin; (d) a decrease in γ -globulin.

3. Administration of concentrated serum albumin daily for long periods resulted in some cases in an increase in albumin, and usually a decrease in β -, α_2 - and sometimes α_1 -globulin concentrations. However, the changes were not maintained after albumin therapy was discontinued.

4. In nephrosis the urine may contain all of the protein fractions present in plasma except fibrinogen. Administration of concentrated human serum albumin intravenously results in an increase primarily in albumin excretion, although minor changes in the excretion of the globulin fractions may occur.

Ascitic and pleural fluids from children with nephrosis have a slightly different distribution of protein fractions than plasma samples from the same children.

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THE LET-DOWN REFLEX IN HUMAN LACTATION

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THE distinction between the secretion and the ejection of milk was first pointed out by Gaines.¹ The secreting animal must actively expel the milk; this is shown by the fact that the milk which is known to be present in the gland is only partly available to ordinary milking manipulations in anesthetized,^{1, 2} or distracted animals,³ or in udders which were excised and perfused,⁴ or amputated at slaughter.^{5, 6}

The mechanism by which milk is made available has been variously described as let-down (cows), draught (women), or the ejection, expulsion, or pumping reflex. It has been extensively investigated in domestic animals but few details are available as to its nature in the human species.

Let-down has been shown to be a reflex process, and, as a result of considerable investigation, Ely and Petersen³ postulate the following mechanism: Nerves in the teat are stimulated by sucking or milking; impulses which cause the release of the oxytocic principle of the posterior pituitary gland are carried to the central nervous system. This substance reaches the breast by the blood stream and causes contraction of the smooth muscle surrounding the alveoli. Thus the contents of the alveoli are forced into the large ducts where they are available to the young or to the milking machine. In addition to the direct stimulus of sucking, psychic factors such as preparations for milking may initiate the reflex.

There is some evidence that a let-down reflex occurs in women.^{7, 8} If a baby pulls away from a full breast for a moment, the milk may sometimes be seen to spray out of its own accord for a distance of several inches. Some women report subjective sensations during let-down, and milk may be observed to drip from the breast opposite that being sucked. It seems reasonable to suppose that the same mechanism occurs in women as in animals, and this investigation represents a preliminary attempt to test the correctness of Petersen's theory on a lactating woman.

METHODS AND RESULTS

The physical and psychologic difficulties of performing experiments on human lactation are many. It is for this reason that we feel justified in presenting the results of well-controlled studies on one subject.

The subject was a 25-year-old woman who was in good health. She had already successfully breast-fed one baby for eleven months. Her second child was a healthy, full-term girl weighing 7 pounds, 8 ounces at birth. She was entirely breast-fed on a self-demand schedule from birth. At the beginning of the study she was 7 months old, in good health, and weighed 19½ pounds. She was taking four to five breast feedings a day with a daily supplement of solid food and orange juice (about 250 calories). Both mother and child were well throughout the period of study.

The major part of the investigation was designed to show if the let-down reflex can be inhibited by distraction of the mother, and if a normal yield of milk can be obtained by combining a distraction with an injection of the oxytocic principle of the posterior pituitary gland.

It was established by preliminary experiments that the baby would take a relatively constant amount of milk at the first feeding in the morning under the following standard conditions: (1) the mother was basal; (2) only the right breast was used; (3) nursing time was limited to ten minutes; (4) the baby had not been fed for at least ten hours previously; (5) the baby had been awake for at least forty-five minutes, since it was found that she did not become hungry before that time; (6) every attempt was made to prevent the baby from crying before she was taken in to nurse, since crying produced premature let-down; (7) the baby was weighed before and after nursing, the difference in weight being the amount of milk taken. The scales were marked to measure to within $\frac{1}{4}$ oz. and with practice weights could be gauged to within $\frac{1}{8}$ oz. (3.5 Gm.). The amount of milk taken was recorded to the nearest gram. All these conditions were fulfilled in every experiment. The fact that a consistent amount of milk was taken under these circumstances is shown by the mean figure of 194 Gm. of milk taken in fifteen preliminary experiments with a range of 177 to 219 Gm. and a standard deviation of 11 Gm.

Three types of experiment were performed: controls, distraction plus injection of saline, and distraction plus injection of Pitocin.* On control mornings mother and baby were not disturbed during the ten-minute nursing period. On distraction mornings a distraction was started about four minutes before the baby was due to be brought in. Two minutes later an injection of 0.3 c.c. of either Pitocin or sterile saline was given intramuscularly. The distraction was continued until the baby was brought in, and throughout the nursing period. The subject was not told beforehand whether the injection was to be of Pitocin or saline. The dose of Pitocin was determined after trials; an effect was produced by as little as 0.1 c.c., while 0.3 c.c. consistently produced a sensation of let-down in thirty to ninety seconds which was stronger than that produced by the baby sucking. No ill effects were observed in mother or baby from this dose of Pitocin.

The nature of the distraction to be used presented some problems, since distraction of the baby from sucking was undesirable; also, the mother was not easily prevented from letting down her milk and tended to become accustomed to any particular distraction if used on two or more successive days. It was finally decided to use three distractions. These were: (1) immersion of the feet alternately for ten seconds out of every thirty in ice water (The subject stated that this was the worst distraction.); (2) a combination of electric shocks of moderate intensity with a rapid series of questions involving mathematical problems (The shock was given when an incorrect answer was returned or the subject delayed more than ten seconds before replying. This distraction was effective in disturbing the subject emotionally and making her angry, although the

*Parke, Davis & Company posterior pituitary preparation containing 10⁶ units of oxytocic substance per cubic centimeter.

effect was diminished when the baby was seeking food at her breast. It was noted that she then tended to have difficulty hearing the questions and frequently delayed answering.); (3) a length of surgical bandage was attached to each of the subject's big toes and pulled intermittently, causing sharp pain from the stretching and the tightness of the gauze around the toe.

The results of these experiments are shown in Table I. The mean amount of milk taken by the baby on distraction-plus-saline days is significantly lower than that taken on control days and significantly lower than that taken on distraction-plus-Pitocin days. The amount taken on distraction-plus-Pitocin days is lower, but not significantly so, than that taken on control days.* This eliminates the possibility of significant distraction of the baby, although it is likely that she was slightly affected by the proceedings. In the case of each individual distraction, the figures for the distraction plus Pitocin are higher than those for distraction plus saline.

TABLE I. EFFECT OF DISTRACTIONS, AND DISTRACTIONS PLUS INJECTION OF 0.3 C.C. PITOCIN ON AMOUNT OF MILK TAKEN BY BABY IN TEN MINUTES

CONTROL		DISTRACTION PLUS SALINE			DISTRACTION PLUS PITOCIN		
DATE	GM. MILK TAKEN	DATE	TYPE OF DISTRACTION	GM. MILK TAKEN	DATE	TYPE OF DISTRACTION	GM. MILK TAKEN
5- 1	153	4-29	TP	96	5- 7	TP	146
5- 2	177	5-20	TP	134	5-11	TP	170
5- 5	163						
5- 9	181	5- 4	IW	64	4-30	IW	127
5-12	142	5-15	IW	71	5- 8	IW	149
5-14	163						
5-19	209	5- 6	ED	113	5- 3	ED	174
5-21	153	5-10	ED	113	5-16	ED	156
Means	168			99			153

TP = Toe Pulling.

IW = Ice Water.

ED = Emotional Disturbance.

The second series of experiments were designed to illustrate the existence of the let-down reflex in a different manner. The left breast which was producing comparatively little milk was pumped by means of an electric breast pump at the same intermittent suction pressure for ten minutes either four or eight hours after it had been emptied by either the baby or the pump. One minute later the baby was put to the right breast. After the baby had sucked for one minute the breast pump was reattached and the left breast pumped for a further five minutes. In control experiments a two-minute interval was inserted between the two periods of pumping and the baby was not put to the right breast.

The results of these experiments are shown in Table II. Although the number of experiments is small, it will be seen that in each case, when the baby was applied to the right breast between the periods of pumping, the yield of milk in the last five minutes was much greater than that in the first ten minutes. In the control experiments it was less. It was noted that at no time did the mother feel a sensation of let-down to the breast pump alone, but a definite

*In these experiments a difference is considered significant if the possibility of the same or a greater difference occurring by chance is less than one in 100 ($p = 0.01$ using Student's t for calculation of the differences between means in small samples).

sensation of let-down was felt about sixty seconds after the baby began to suck vigorously. The fact that the mother did not let down to the breast pump is, perhaps, not surprising in view of the finding that wild animals who have been accustomed to suckling their young will let down their milk only with great difficulty to milking manipulations."

TABLE II. EFFECT OF APPLYING BABY TO RIGHT BREAST ON YIELD OF MILK FROM LEFT BREAST TO A BREAST PUMP

DATE	HOURS SINCE LEFT BREAST EMPTIED	YIELD OF MILK IN CUBIC CENTIMETERS	
		0 10 MINUTES	12 17 MINUTES
(a) Baby on Opposite Breast			
5 13	8	3	11
5 16	3½	7	19
5-16	5	2	5
5 20	3	7	21
5 24	3½	2	7
Means		4	13
(b) Controls			
5 14	8	7	1
5 17	4	8	2
5 18	4½	4	2
Means		6	2

The third series of experiments was designed to show whether the effect of putting the baby to the breast could be duplicated by injections of Pitocin. All experiments in this series were performed at about the same time of day. The left breast was pumped for ten minutes approximately eight hours after the baby had last nursed at it. The same breast pump and suction pressure were used as in the second series of experiments. One minute later Pitocin (0.3 c.c.) was injected intramuscularly. After waiting one minute, pumping was again performed for five minutes. On control days 0.3 c.c. of sterile saline was injected instead of the Pitocin. The subject was not informed of the nature of the injection.

TABLE III. EFFECT OF INJECTION OF 0.3 C.C. PITOCIN ON YIELD OF LEFT BREAST TO BREAST PUMP

DATE	HOURS SINCE LEFT BREAST EMPTIED	YIELD IN CUBIC CENTIMETERS	
		0 10 MINUTES	12 17 MINUTES
(a) Pitocin			
4 26	8	11	26
4 29	7	9	20
4 30	7	9	27
Means		10	24
(b) Control			
4 28	7½	8	2
5 2	8½	10	4
5 6	8½	11	4
Means		10	3

The results of these experiments are given in Table III. The amount of milk produced during the first ten minutes was very constant in all experiments. However, Pitocin produced eight times as much milk in the second period as did saline. Pitocin injections were always followed in from thirty to ninety seconds by a subjective sensation of let-down which was more pronounced than

the normal let-down to the baby. Drops of milk appeared at that time on the nipple of the right breast which was not being pumped. It may be noted that the yield obtained after Pitocin was somewhat higher than that obtained after placing the baby on the other breast.

DISCUSSION

Inhibition of the eentral part of the let-down reflex has been produced in cows by Ely and Petersen.³ Animals who were frightened or emotionally disturbed did not let down their milk. Our experiments show that a similar eentral inhibition can be produced in woman. Severe cold, emotional conflict (electric shock experiment), and pain significantly decreased the yield of milk. Inhibition is typical of a reflex mechanism. In other experiments not reported in detail the inhibition was at least partially overcome by the subject's taking a small amount of alcohol forty-five minutes previously. In two experiments the mean yield of the left breast to the breast pump in ten minutes was increased from a control figure of 10 c.c. to 21 c.c. In two other experiments of the same type the inhibition was restored in spite of the alcohol due to anger and embarrassment on the part of the subject; in these instances the mean yield was reduced to 6 c.c., or below the control figure.

It has been clearly shown that the efferent pathway of the let-down reflex is hormonal rather than nervous. Ely and Petersen³ divided two out of three nerves to one side of the udder in three cows and showed that the yield was equal to that on the intact side. Petersen and Ludwick⁴ showed that blood taken from a cow who had been stimulated to let down her milk would produce let-down when perfused through an isolated cow's udder, while blood taken from a cow not stimulated to let down had no effect.

It seems probable that the hormone responsible for the effect of the let-down reflex is produced by the posterior pituitary gland. The part played by this gland was first noted by Ott and Scott,¹⁰ who found that injections of whole posterior pituitary extract greatly increased milk flow over a short period of time in a goat. This was confirmed by Mackenzie in cats,¹¹ Schafer in women,¹² Turner and Slaughter in cows,¹³ and others. Gomez^{14, 15} more definitely identified the action of the posterior pituitary. In hypophysectomized rats in whom milk secretion was maintained by injections of anterior pituitary lactogenic hormone and adrenal cortical hormone, the young failed to obtain milk although they sucked vigorously. With the addition of injections of posterior pituitary extract the young were able to obtain milk and thus survived. The observation by Smith¹⁶ and Honnssay¹⁷ that successful lactation can occur after removal of the posterior pituitary is difficult to reconcile with this. However, it is possible that posterior pituitary hormones may be formed elsewhere than actually in the gland.

It is not certain exactly which posterior pituitary hormone is responsible for the effects. Ely and Petersen³ found that normal let-down could be produced by injections of either the oxytocic or the pressor factor in distracted cows, but that in small doses the oxytocic factor was more effective. Petersen¹⁵ showed the oxytocic principle to be effective in isolated, perfused udders. Our

experiments show that the oxytocic principle (Pitocin) has a similar effect on let-down in woman. Distraction plus Pitocin produced a normal yield, while in the breast pump experiments Pitocin produced an increase in milk flow similar to that produced by the application of the baby to the other breast. Turner and Cooper¹⁹ showed that the pressor factor had some activity in causing let-down in the lactating rabbit. They suggested that possibly an unknown substance present in both pressor and oxytocic factors may be concerned. Petersen¹⁸ tried the effect of various substances on let-down in isolated perfused udders and found that complete let-down was produced by Pitocin and acetylcholine, and that partial let-down was produced by Pitressin (pressor factor), epinephrine, histamine and acetyl- β -methylecholine.

It is not certain how the posterior pituitary hormone acts on the mammary gland. The most likely explanation is that it causes contraction of the smooth muscle fibers surrounding the alveoli. This was first suggested by Gaines,¹ using whole posterior pituitary extracts, and has been more recently advocated by Ely and Petersen,³ using the oxytocic principle. This latter substance is known to cause contraction of smooth muscle elsewhere in the body, especially in the uterus, and its action on the breast would not be unexpected. However, there is considerable doubt about the existence of muscle fibers around the alveoli in animals, although Swanson and Turner²⁰ report finding them in the gland of a lactating cow. Muscle fibers have not been demonstrated in the human breast. Some additional evidence that the contents of the alveoli are actually forced out during let-down in woman is advanced by Waller⁸ on the basis of fractional milking studies. He found that the hind-milk contained more fat than the fore-milk, which suggested a rapid forcing of milk and fat from the alveoli through the duct system.

Our results support the idea that Petersen's theory of the mechanism of let-down in animals holds for the lactating woman. It is interesting to speculate on the possible application of this knowledge to breast feeding in general. Many mothers are nervous about feeding their first baby; they are upset by the strange hospital surroundings; they are embarrassed by having to expose their breasts among strangers; their nipples are often sore and their breasts engorged. Emotional disturbances, embarrassment, and pain inhibit let-down to the sucking baby, and thus the baby gets little milk.

Furthermore, sucking itself is the primary stimulus which sets off the let-down reflex. Babies, brought to their mothers at scheduled times, may be so worn out with crying or so sleepy that they probably do not suck as vigorously as if they were applied when they woke up spontaneously and first sought food.

A vicious cycle is thus set up. Absence of let-down leads to more engorgement and more engorgement makes it all the more difficult for the baby to suck. Experiments by Gunther²¹ on the effect of sucking show that when a baby sucks without getting milk for periods of over two minutes, characteristic erosive or petechial lesions of the nipple are produced. The mother often states that it feels as if the baby is biting her. In our experiments it was noted that when the baby sucked for prolonged periods without getting much milk (as in the ice-water distraction experiments) the mother's nipples were sore for some time afterward. It is likely that lesions of the nipple so produced may eventually

lead to complications such as breast infections and breast abscesses. Such misfortunes might well be averted by the administration of Pitocin and emptying the engorged breast by a breast pump or a hungry baby.

SUMMARY

1. The mechanism of the let-down reflex in human lactation has been studied.
2. The reflex can be inhibited centrally by distractions which affect the mother and not the baby.
3. This inhibition can be overcome by the intramuscular injection of Pitocin (posterior pituitary extract).
4. Application of a baby to one breast produces a great increase in the flow of milk from the other breast.
5. Intramuscular injection of Pitocin produces an increase in the flow of milk similar to and accompanied by the same subjective sensations as those produced by applying the baby to the other breast.
6. The significance of these findings in relation to breast feeding as a whole is discussed.

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OLLIER'S DYSCHONDROPLASIA

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OLLIER'S disease is a developmental abnormality affecting the growing ends of long bones. It is characterized by malformation of the ends of the shafts, consisting of masses of unossified cartilage in the diaphyses. In most cases the condition is present in only one extremity or in both extremities of the same side of the body. It may affect the long bones of the hands and feet. This case is reported to demonstrate (1) the unilateral feature of the disease, (2) the x-ray appearance of the lesions.

CASE REPORT

The patient, a white female child aged 3 years, was admitted to the Fort Hamilton Station Hospital, March 30, 1948, with a chief complaint of "one hip higher than the other." One year previously it had been noted that the child limped slightly. The limp grew progressively more pronounced and the pelvis was tilted to the right at the time of admission. At birth it had been noted that the dorsum of the left hand was puffy in appearance. It was felt that the puffiness had increased markedly during the previous year. The history revealed no other abnormalities of birth or neonatal period. The child had an adequate diet and supplementary vitamin intake. The family history was noncontributory.

Physical examination showed a 3-year-old white female who was alert, cooperative, and in no distress. The positive findings were limited to the extremities. The dorsum of the left hand was puffy in appearance, nonpitting, and the transpalmar measurement was 5.5 cm. The right hand appeared to be normal, with a transpalmar measurement of 4.75 cm. The left leg measured 41.25 cm., the right leg 36.9 cm., from the anterior superior spine to the internal malleolus. In the erect position the left gluteal fold was higher than the right and there was an obvious tilt of the pelvis to the right. There were no palpable tumors in the extremities. The child walked with a moderate limp.

Laboratory findings were as follows: Urinalysis, negative; hemoglobin, 13.0 Gm.; red blood cells, 4,350,000; white blood cells, 10,400, neutrophils 36, lymphocytes 58, monocytes 3, eosinophiles 3; throat culture, alpha streptococcus and neisseria; blood studies, Kahn negative, cholesterol 201.4 per cent, total proteins 7.20 Gm. per cent, albumin 4.31 Gm. per cent, globulin 2.89 Gm. per cent, phosphorus 4.0 mg. per cent, alkaline phosphatase 8.3 Bodansky units, calcium 10.1 mg. per cent.

X-ray Studies.—Considerable information was obtained from the radiographic examination. The outstanding roentgenologic findings consisted of unilateral bone changes, characterized by nonossified areas of rarefaction alternating with areas of normal ossification. This was most evident in the diaphyses of such long bones as the humerus, radius, femur, and tibia on the right side. Similar bone changes were also demonstrable in the scapula, os pubis, and first metatarsal and phalanges of the right foot. Worthy of note was the oblique and longitudinal arrangement of the lesions in relation to the shaft, as well as the occasional involvement of the epiphyses. The lesions are medullary as well as cortical. The roentgenologic picture is highly suggestive of a disturbance of the normal osteogenesis rather than a congenital anomaly. In this case no deformities of the bones were detected except

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Fig 1—Right hip, showing bone defects of the upper portion of the right femur, including the neck and head. The absence of cortical ossification and changes in the bone texture are also present in the right pubic bone. Pelvic tilt is secondary to lower extremity. The left hip appears to be normal.

for early widening and tortuosity of the metaphyseal portions of the femur and tibia. The soft tissue shadows show no atrophy or tumefaction. The corresponding structures of the left side are essentially normal.

The clinical picture of this patient remained essentially unchanged during her hospital stay.

DISCUSSION

In Ollier's disease the normal ossification of cartilage in the affected ends of the bones is retarded and the unossified cartilage remains in the diaphyses. Ossification is prevented by the lack of normal degeneration and calcification, though some calcification may occur in parts of the periphery but without the changes of normal enchondral ossification. The cartilage in the diaphyses generally proliferates normally, but may occasionally take on independent growth leading to the formation of huge tumors, and consequent deformities. Since



Fig. 2.

Fig. 3.

Fig. 2.—Right knee, showing longitudinal and oblique areas of rarefaction due to unossified cartilage, these areas are present in the distal end of the femur and proximal end of the tibia. Epiphyseal involvement is also apparent. Left knee shows normal bones.

Fig. 3.—Right ankle, showing similar changes of the tibial metaphysis and epiphysis. Widening and flaring of the involved portions are precursors to gradual bone deformities. The left ankle is normal.

the lesions are close to the epiphyses, the growth of the limb is usually affected and shortening of the extremity results. The tumors are not true neoplasms but are rather the results of disturbances of the physiologic process of bone growth. The retardation of growth of certain portions of bone with normal growth in adjacent portions results in deformity. In rare instances the lesions have become sarcomatous.

The condition may be associated with other developmental abnormalities. In the case reported here a lymphangioma was present in the left hand.

The onset of symptoms is gradual during the early years of life. An early sign is the limp which develops due to the shortening of the affected lower extremity. Tumor and/or deformity may be the first evidence of the disease. Pain is not associated with the lesions.



Fig 4—Right foot, showing minimal changes with irregularity, coarse trabeculation, and rarefaction in the metatarsals and phalanges of the big toes. The left foot is normal



Fig. 5—Right forearm, showing lesions in the right radius. Apparently normal ossification has been re-established in the growing portion of the bone. The left forearm is normal.

The diagnosis is established on the roentgenologic findings.

Treatment.—Orthopedic management for prevention or correction of secondary deformity is the only therapy of value.

SUMMARY

A case of Ollier's dyschondroplasia, involving the right scapula, humerus, radius, os pubis, femur, tibia, first metatarsal, and phalanges has been presented. The left side of the skeleton is not involved.

The disease is a developmental abnormality characterized by the presence of masses of unossified cartilage in the diaphysis of long bones. The lesions are generally unilateral in distribution.

The diagnosis is established on the roentgenologic findings.

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THE THERAPEUTIC USE OF PERITONEAL LAVAGE FOR ANURIA CAUSED BY TOXIC NEPHRITIS

REPORT OF A CASE

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SEVERAL papers have described the use of peritoneal lavage for the treatment of anuria resulting from such conditions as sulfonamide blockage, transfusion reactions, and mercury poisoning.^{7-10, 12, 13} The purpose of this report is to emphasize the case with which the procedure may be carried out and to describe its use in an additional case of toxic nephritis associated with pneumonia.

REPORT OF A CASE

M. H. was an 11-month-old white male infant admitted to Strong Memorial Hospital on Dec. 23, 1947, because of the sudden appearance of cyanosis and coma one hour before admission. He had a cough and nasal discharge for one week, and three days later developed wheezing respirations and fever. A physician prescribed Dover's powders to be given four times a day and advised the forcing of fluids. He improved and was free of wheezing until the evening of the fifth day of the disease, when wheezing began again and the temperature increased. Three days before admission he passed green, watery stools. Urination was normal. On the morning of admission, the patient's condition was unchanged. He retained his morning bottle feeding and moved about his crib. At 11 A.M. he was found unconscious, pale, and cyanotic, with rapid, panting respirations.

His mother had hypertension and edema during pregnancy. The infant, born two weeks after term, weighed 11 pounds. His development was normal. He received orange juice but no other vitamin supplements. He had no other serious infections previously, and had received no immunizations. There was no history of allergy. The family history was irrelevant.

Physical examination disclosed a well-developed, obese white male infant in a moribund state. The eyes were rolled up, the pupils were constricted. Respirations were deep, sighing, and regular, at the rate of 68 per minute. The blood pressure unfortunately was not recorded at any time during his hospital course. The skin was hot and dirty. Cyanosis was observed only in the nail beds. Both eardrums were injected but not bulging. The neck was supple. Over the right base posteriorly there were dullness to percussion, moist râles, and bronchial breath sounds. A to-and-fro friction rub was audible in the right axilla. Elsewhere, breath sounds were harsh with many audible rhonchi. The heart was not enlarged to percussion and no murmurs were audible, but the sounds were obscured by the noisy respirations. The liver was palpable 2 cm. below the right costal margin. No other organs were palpable.

On admission the red blood count was 3.5 million, the hemoglobin 11 Gm., and the white blood count was 51,000 with 57 per cent neutrophils. The urine was normal although only about 5 c.c. was obtained. An x-ray of the chest revealed an acute pneumonic process in the right middle lobe and a suggestion of pneumonia in the left midlung field. The tuberculin skin test was negative. The nose and throat cultures grew pneumococcus Type 19. The serum carbon-dioxide combining power was 15 volumes per cent, the nonprotein nitrogen was 90 mg. per cent, the salicylate level was zero, and the ieterus index was 7 units per 100 c.c.

Course.—Eighteen hours after admission the patient was still moribund although he had received the continuous administration of oxygen and of intravenous fluids, including 300 c.c. of M/6 sodium lactate and 200 c.c. of whole blood, and the injections of penicillin and sulfadiazine. He had passed only a few cubic centimeters of urine. By this time the non-

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protein nitrogen had risen to 127 mg. per cent. His condition seemed hopeless, for he did not respond to any stimuli and appeared to be in peripheral circulatory collapse. (Capsulotomy of the kidneys was considered but dismissed as it was felt that the procedure was too dangerous under the circumstances.) Diathermy to the kidneys and the intravenous injection of aminophylline failed to stimulate the secretion of urine.

At this point, peritoneal lavage was instituted using the technique of Bassett.¹³ A No. 14 mushroom catheter was inserted into the right flank and a sump drain was introduced through a left flank incision by Dr. Paul Schloeb.

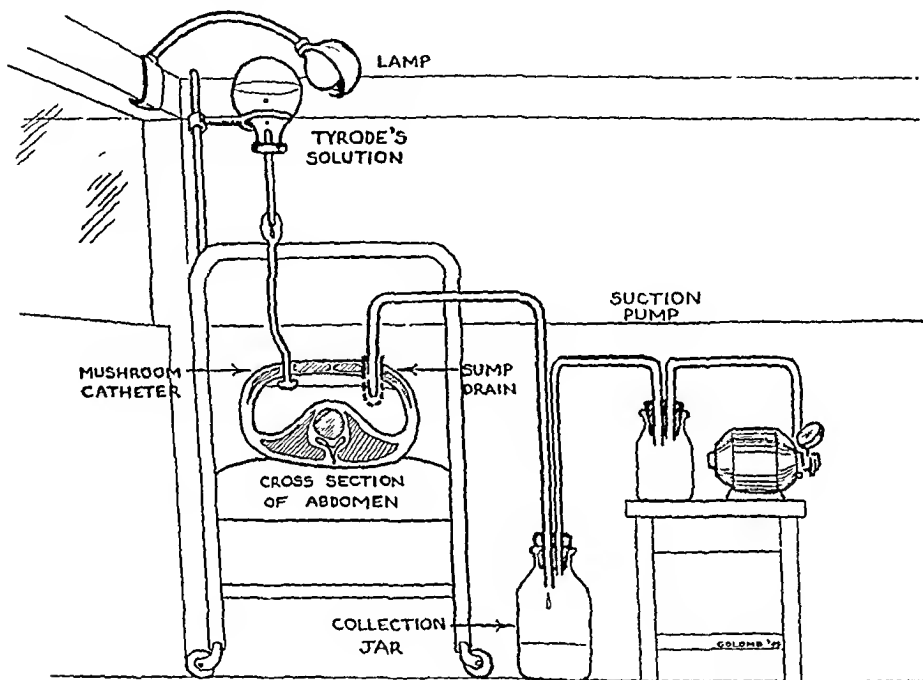


Fig. 1.

During a five-day period, 19,570 c.c. of solution was introduced and a total of 20,020 c.c. withdrawn. The solution used was a modified Tyrode's solution containing, per liter, the following:

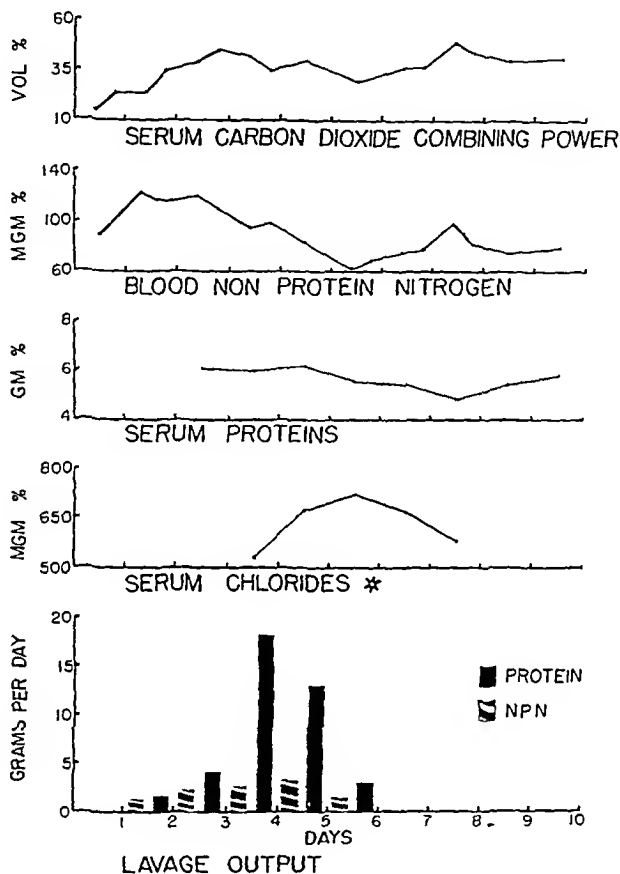
NaCl	9.0 Gm.
KCl	0.2 Gm.
CaCl ₂	0.2 Gm.
MgCl ₂	0.1 Gm.
NaH ₂ PO ₄	0.05 Gm.
NaHCO ₃	0.5 Gm.
Glucose	10-20 Gm.
Penicillin	100,000 units

The NaHCO₃, glucose, and penicillin were added after the autoelaving process.

The salts were calculated for 1,500 c.c. and were weighed in individual paper cups and added to six or eight flasks, each containing 1,500 c.c. distilled water. The flasks were then autoelaved and at least three were kept available for replacement when the previous flask was exhausted. The calculated amounts of NaHCO₃, glucose, and penicillin were added to the solution just before it was to be used.

The apparatus (Fig. 1) included an inverted 1,500 c.c. flask attached to a Murphy drip apparatus and direct tubing from this to the mushroom catheter. The perfused fluid was

then withdrawn from the sump drain by continuous suction into a waste bottle. A gauge on the suction apparatus allowed for regulation of its suction pressure. A heat lamp focused on the solution in the flask kept it at approximately body temperature. The Murphy drip was adjusted to allow the solution to perfuse at the rate of 4 L every twenty four hours.



* expressed as NaCl

Fig. 2

The patient received fluids, including whole blood and human serum albumin, by vein. It appeared unnecessary to add sodium and chloride ions, since these were probably adequately supplied by lavage. Vitamin B complex and ascorbic acid were also administered parenterally. In addition, he received oxygen continuously, Wangensteen suction to control abdominal distension, and 50,000 units of penicillin every three hours subcutaneously. Unfortunately, the amount of fluid withdrawn by Wangensteen suction was not recorded. After the first forty eight hours the patient gradually improved, and by the fourth day was able to take fluids by mouth. He began to urinate by the third day and passed 30 cc of urine on the fourth day. The nonprotein nitrogen gradually dropped until it reached a level of 63 mg per cent on the fourth day. On that day the Wangensteen suction and peritoneal lavage were clamped off and he continued to pass urine up to 32 cc. The following day, the catheter and sump drain were removed and the sump wound was closed by one triple zero catgut suture. On the next day he seemed better and continued to pass urine. During the period when peritoneal lavage was operating he passed no stools but passed one, five and

six stools, respectively, on the first, second, and third postlavage days. The use of oxygen was discontinued on the second postlavage day. The nonprotein nitrogen rose following discontinuance of the lavage but fell again to 77 mg. per cent on the second postlavage day. Later that day a portion of bowel herniated through the sump drain incision. The hernia was reduced by operation and the wound reclosed. The next day the temperature rose to 40.8° C. Streptomycin therapy was begun. *Bacillus aerogenes* was cultured from the blood. The next morning he began to have rapid respirations and shortly thereafter was found dead.

AUTOPSY

(Performed by Dr. H. Tesluk on Jan. 2, 1948, approximately four hours after death.)
Gross.—

General: The pertinent findings were as follows: The peritoneum contained 150 c.c. of clear, yellow fluid. The omentum and a few loops of small bowel were adherent to the under-aspect of the sump drain incision and the peritoneum in this area was covered with granulation tissue showing brownish discoloration. Directly in the midline were several other loops of small bowel which were quite red and edematous and adherent to each other with fibrinous adhesions. Elsewhere there was no peritoneal reaction. There was 100 c.c. of clear, yellow fluid in the left pleural cavity. The right pleural cavity contained no excess of fluid but there were many delicate adhesions between the visceral and parietal pleura over the lower lobe of the lung. The pericardial cavity contained a few cubic centimeters of clear, yellow fluid.

Heart: The heart weighed 75 Gm. and was essentially normal in appearance.

Lungs: The left lung weighed 145 Gm., the right weighed 153 Gm. The left lung showed many small, firm, raised, dark areas of bronchopneumonia. In the upper lobe there were many discrete, white areas a few millimeters in diameter. The pleura of the right lower lobe was granular and many minute ecchymotic areas were scattered over the surface of the lung. The bronchi were edematous. Patches of slightly raised granular areas were seen on section of the middle lobe. The upper lobe showed areas of meaty, airless tissue and several firm, yellow, discrete areas varying from a few millimeters to 1.5 cm. None of them was liquid.

Spleen: The spleen weighed 95 Gm. and was firmer than normal. Prominent malpighian corpuscles were noted.

Gastrointestinal tract: The localized peritoneal reactions of the small bowel have been described. One of these involved about 4 cm. of small bowel and was located in the mid-portion of the ileum. The other area was more extensive, involving 15 cm. of lower ileum. The mesentery of this portion was edematous, hemorrhagic, and covered with fibrin. The nodes were enlarged and soft.

Pancreas: Normal.

Liver: The liver weighed 670 Gm. and was normal except for some swelling and translucency of the parenchyma.

Adrenals: Normal.

Kidneys: The left weighed 123 Gm., the right weighed 115 Gm. The cortex was pale with many small, dilated vessels and a few minute, petechial hemorrhages. On cut section the pallor was striking, striations were faint, and glomeruli were made out with difficulty. No hemorrhages were seen internally. The mucosal lining of the calices and pelves was somewhat roughened and injected. There was some narrowing of the ureteropelvic junction of the left kidney but none of the right.

Pelvic organs: The bladder contained only a few cubic centimeters of rather cloudy urine. The mucosa was shiny and gray and the ureteral orifices were normal.

Brain: The brain weighed 1,050 Gm. There was slight edema and on section there was moderate injection of the vessels in the white matter.

Histological.—

Heart: Normal.

Lungs: One section showed multiple abscesses which were quite large and had necrotic, pale centers surrounded by a zone of neutrophiles, and this in turn by a zone of hemorrhage.

The bronchioles showed sloughing of the epithelium. Other areas showed finely granular exudate in the alveolar spaces. There were frequent areas of hemorrhage. The pleura showed a layer of fibrin on its surface. There was edema of the intima of the pulmonary arteries with inflammatory infiltration.

Spleen: The spleen showed a healing infarct and many neutrophiles in the pulp.

Gastrointestinal tract: Section of the small bowel involved in the evisceration showed injection, hemorrhage, and edema. Section of the left abdominal incision showed necrosis, edema, and granulation tissue involving skeletal muscle with sutures and foreign body reaction.

Adrenal: Edema and one small area of necrosis in the cortex were noted.

Kidneys: There was marked interstitial edema and frequent focal collections of round cells in the stroma. The edema seemed to involve loops of the glomerular tufts. Tubules in the cortex were dilated and lined by flattened, pale-staining epithelium which contained no fat. In a few areas epithelial cells had proliferated to form projections into the lumen.

Brain: This was normal except for the presence of clumps of bacteria in a few blood vessels.

Cultures: The post-mortem cultures of the lungs showed *B. aerogenes*.

The sections were reviewed by members of the Department of Pathology. They believe that the necrotizing pneumonia had been going on for some time and was the primary pathologic process responsible for death. The changes in the kidney were apparently secondary to the acute pulmonary infection and appeared to be a combination of acute interstitial nephritis and subsiding tubular degeneration.

COMMENT

A case of severe necrotizing pneumonia in an 11-month-old male infant complicated by toxic nephritis with anuria is described. Death resulted from septicemia caused by *B. aerogenes*, secondary to postoperative herniation of small bowel through the sump-pump incision. Whether or not he might have survived, had streptomycin been started immediately upon discovery of the herniation, is a matter of conjecture. Although the patient died, it is probable that the anuria associated with toxic nephritis was corrected by peritoneal lavage as indicated by the favorable clinical response, by the continued fall of the blood nonprotein nitrogen values after its institution, and by the evidence of healing tubular degeneration found at autopsy. As illustrated in the accompanying graph, the response of the nonprotein nitrogen to the procedure was both prompt and sustained. The same chart illustrates an astonishing loss of protein in the peritoneal lavage fluid. Although human serum albumin was supplied to replace the protein loss, it failed to completely compensate for the large loss resulting from lavage. An entirely satisfactory explanation of this loss of protein is not available. However, it is well known that the peritoneal surfaces of infants are permeable to protein molecules, an observation which has led to the use of intraperitoneal blood transfusions in them. Moreover, the gastrointestinal tract of infants is also known to be particularly permeable to protein molecules.

Another problem which arose in our study was the correction of acidosis which required the frequent parenteral administration of alkali. The blood chlorides rose to a high level during lavage, but returned to normal when the glucose concentration of the lavage fluid was adjusted to correct a moderate dehydration. The serum phosphorus values ranged between 3.9 and 5.0 mg. per cent, while those for calcium varied between 7.1 and 8.0 mg. per cent.

The history of the use of peritoneal lavage began many years ago. The earlier observers^{1, 2, 3} used an injection-withdrawal technique with a time lag between injection and withdrawal. By this method, Bliss and co-workers¹ kept nephrectomized dogs alive for thirteen to sixteen days, compared with a survival time of two to three days for the untreated dogs. By the same method,² rabbits given bichloride of mercury showed a far greater recovery rate following peritoneal lavage. Rhodes³ used this method in two human subjects. Although the patients failed to survive, they showed a temporary fall in blood urea nitrogen.

The first successful use of continuous lavage in man was by Wear.⁴ He used two trocars, one a standard gall-bladder trocar in the upper abdomen, and the other a trocar with numerous perforations in its distal end to avoid occlusion by omentum and intestines. The perfusion fluid was Locke-Ringer's solution. One of the three patients on whom this method was used, survived. He had renal shutdown secondary to bladder calculi and benign prostatic hypertrophy.

The preferred type of fluid was discussed by Abbott and Shea.⁵ They found that a perfusion solution with a chemical consistency closely similar to that of interstitial fluid was the most suitable for lavage.

Seligman, Frank, and Fine⁶ were the first to use Tyrode's solution. They treated nephrectomized dogs and included penicillin, sodium sulfadiazine, and heparin in their therapy. They calculated the blood urea clearance by peritoneal lavage to 41 to 48 per cent of the average renal clearance. They found the efficiency of peritoneal dialysis of urea to be one-third to one-half that of glomerular filtration. This did not take into consideration tubular reabsorption of urea. As a result of the clinical use of their method^{7, 8} one out of four patients survived.

The indication for peritoneal lavage is temporary anuria resulting from toxic nephritis, sulfonamide toxicity, transfusion reaction, heavy metal poisoning, and any other condition which causes temporary anuria. It is realized that considerable difficulty may arise in judging whether anuria in a given patient is temporary or permanent; and, if temporary, in deciding the proper time to start the procedure. At any rate, peritoneal lavage is a means of combating temporary anuria which successfully lowers the increasing level of nitrogenous waste products in the blood stream. The high mortality of the patients treated with this procedure in the past may have been related in part to the severity of their illness prior to its initiation.

In the future the technique of continuous peritoneal lavage should improve with experience. The use of the mushroom catheter and sump pump has been found by several observers^{9, 11} to offer a greater advantage than that of the mushroom catheters alone or that of trocars. Using this technique we had no difficulty with blockage of flow from omentum or bowel as was experienced in the case discussed by Bloxsum and Powell.¹²

Although heparin may be indicated in certain instances, it was found unnecessary to use this anticoagulant in our case. It is also probable that streptomycin should be administered to combat infections caused by gram-negative organisms.

The procedure described here can be set up in any modern hospital with a minimum of effort. The insertion of the draining tubes can be done safely at the bedside under aseptic conditions. The prompt use of streptomycin in the event of postoperative bowel herniation is suggested.

CONCLUSIONS

1. A case of toxic nephritis with anuria treated by peritoneal dialysis is described.

2. The simplicity of the apparatus is emphasized and its more general use in similar cases of temporary renal shutdown is urged.

The author is indebted to Miss Elizabeth Day and to Mr. Fred Golomb who prepared the graph and diagram.

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TOPICAL AND PARENTERAL PENICILLIN THERAPY IN RITTER'S DISEASE

REPORT OF FOUR CASES WITH RECOVERY

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FOR many years the entity known as "Ritter's Disease" has carried with it an extremely high mortality. Most authors report a rate of 48 to 52 per cent; some, however, report a rate as high as 76 per cent. Herein is reported a series of four consecutive patients treated with topical and parenteral penicillin with a resultant 100 per cent survival.

CASE REPORTS

CASE 1.—O. W., a white male infant, was admitted to Children's Hospital at 9 days of age. He was the product of an eight-month pregnancy which was terminated by an eight-hour uncomplicated labor. There were no infections or illnesses during the pregnancy, the only maternal complication being varicose veins of the legs. Oxygen and resuscitation were necessary at birth because of temporary failure of spontaneous respirations. Circumcision was deferred because the baby failed to gain weight as well as expected. Upon discharge from the hospital five days after birth the parents noted the face to be red and sore; this they attributed to scratch marks. The rash was first noted about the angles of the mouth and soon spread over the remainder of the face. By the seventh day of life the entire body had become involved with marked redness and "peeling" associated with a "yellowish" staining of the baby's clothes. He had been breast fed until the day of admission, when blood came from the breast, prompting the mother to institute an evaporated milk formula.

The past and the family histories were entirely negative. There was no family history of syphilis nor was there a history of the use of strong cleansing or disinfecting agents or the use of any drugs by the mother or infant.

The physical examination disclosed a fairly well-developed 9-day-old white male infant with marked redness and severe desquamation of the skin of the entire body. Many areas were denuded and markedly inflamed. These were more marked over the face, neck, buttocks, scrotum, hips, ankles, feet, and upper and lower thirds of the trunk. The nose, mouth, and throat were mildly inflamed. Upon rubbing islands of apparently normal skin, the epidermis peeled away disclosing raw, inflamed derma (Nikolsky's sign). The lungs were clear to percussion and auscultation and respirations were sixteen per minute. The heart had a normal rhythm and rate and the remainder of the physical examination was essentially negative. The temperature on admission was 100° F. by rectum. A white blood count of 35,000 with 33 per cent eosinophiles was obtained on admission. A skin lesion culture on admission showed hemolytic *Staphylococcus albus* and a skin lesion smear at the same time showed many gram-positive diplococci and a few gram-negative bacilli.

Treatment consisted of the removal of all clothing from the infant, including the diapers, the placing of a heat cradle continuously over his body, and the administration of penicillin intramuscularly with an initial dose of 100,000 units followed by 50,000 units every three hours. Penicillin ointment was placed generously over the entire body every six hours. Supportive fluids and vitamins in large dosages were also used throughout the entire hospital stay. Intramuscular penicillin was continued for nine days and the ointment, heat cradle, and supportive measures for fifteen days.

From the Children's Hospital, Washington, D. C.

During the hospital stay there was increasing exfoliation with the fever reaching a peak of 101.2° F. on the second day. Later, as the erythema of the face began to subside, the desquamation progressed over the entire body. Four days after admission the patient appeared much improved with the exception of a few small areas of desquamation. By the ninth hospital day the skin appeared normal and the intramuscular penicillin was discontinued. On the fifteenth hospital day all other medications were discontinued and on the twenty-fourth day he was discharged, completely recovered.

CASE 2.—J. R., a white male infant, was admitted to Children's Hospital on the sixth day of life. He was the product of a full-term pregnancy, during the second month of which the mother had had pityriasis rosea. At the age of 3 days a scratch was noted on the baby's face and on the following day this scratch was surrounded by an erythematous rim. A generalized fine desquamation of the skin was also present. On the fifth day scaly and erythematous lesions were noted on the hands and forearms. These became larger and confluent and by the time of hospitalization had spread over most of the body surface.

The family history other than that mentioned previously was irrelevant. Syphilis was denied, as was the use of any drugs or harsh agents for cleansing or disinfection.

The physical examination revealed a well-proportioned newborn boy appearing moderately ill with marked erythema, scaling, and desquamation of the face and body being more marked in the axillary folds and folds of the thighs. The scalp contained a few areas of scaling. These areas contained vesicles and bullae with serous fluid as well as crusting patches. Nikolsky's sign was positive. The eyes, ears, and nose were normal and the throat was moderately injected. The remainder of the physical examination was negative. A hemogram was essentially normal, showing 8,900 leucocytes with 7 per cent eosinophiles. A blood culture showed hemolytic *Staph. aureus*. Kahn and Mazzini tests for syphilis were negative. The temperature was normal during the entire hospital stay.

Treatment consisted of 30,000 units of penicillin given intramuscularly every three hours and the application of penicillin ointment to the skin lesions. Two days after admission a heat cradle was utilized and the fluid intake increased. At that time daily administration of 100 mg. of vitamin C and one cubic centimeter of soluble vitamin B was begun. The penicillin ointment was discontinued on the fifth hospital day and the intramuscular penicillin and other medications were discontinued on the seventh hospital day.

The desquamation continued for four days, after which the erythema gradually diminished and re-epithelialization of the skin occurred. On the eighth day the patient was discharged in good condition.

CASE 3.—G. C., a white male infant, was admitted to Children's Hospital when 6 days of age. He was the product of a normal, full-term pregnancy and an uncomplicated labor. Two days prior to admission he developed a generalized erythematous rash, following a fine desquamation of the skin. The rash first appeared on the face and about the mouth and spread to the creases of the groin, axilla, and neck. The erythematous patches rapidly increased in size until the entire body was involved. One day before admission a mild diarrhea developed.

The past and family histories did not reveal the use of any drugs or cleansing agents nor was there a history of allergy, heart disease, skin disease, or venereal disease.

The physical examination disclosed a well-developed and -nourished newborn white male infant in no acute distress. The entire skin was markedly inflamed and exfoliation was noted on both cheeks and on the forehead. The patches of exfoliation measured up to 5 by 8 cm. in size. The outer layers of skin could be removed easily by gentle rubbing, leaving an underlying, raw, red derma resembling a second-degree burn. The exfoliations were most prominent in the right anterior cervical fold, left groin, and left popliteal space.

Treatment consisted of intramuscular penicillin, 30,000 units every three hours, and topical penicillin ointment applied every eight hours. In this case a protein milk formula was used on admission; however, this was soon replaced by evaporated milk. One cubic centimeter of vitamin B complex was given daily. The intramuscular penicillin was discontinued on the fifth hospital day and penicillin ointment on the seventh day.

Within a few days after admission the scaling had extended over the entire body, vesicles and bullae had appeared, and serous fluid was noted beneath the areas of desquamation. By the sixth day the skin was entirely denuded and new areas of normal skin had begun to appear. On the seventh hospital day all medication was stopped and on the tenth day the patient was discharged, the skin being entirely normal.

CASE 4.—S. M., a white female infant, was admitted to Children's Hospital when 3 weeks of age. She had been well until three days prior to admission when she developed "small white pimples" on her buttocks. On the following day a fine desquamation appeared in the same region and shortly thereafter this was noted on the neck, face, ears, and in the axillae. One day before admission a physician prescribed mineral oil and a "tar paste" preparation for application on the involved areas. She had been breast fed since birth and the mother had taken no drugs or medications for more than one year. Neither orange juice nor cod liver oil had been a part of the infant's diet. The patient had been bathed exclusively in olive oil since birth with the exception of the mineral oil mentioned previously. No history of contact with cosmetics, new clothes, or other possible irritants could be elicited. She had been the product of a full term, normal pregnancy followed by an uncomplicated labor and delivery. There were no neonatal complications. The family history was irrelevant. No history of venereal disease could be elicited.

The physical examination revealed a well proportioned, restless white female infant with a generalized scaly rash over the face, neck, buttocks, and axillae. Discrete vesicles filled with clear fluid were noted over the skin of the face and scalp. Some of these had ruptured, leaving crusts, and many crusts were present in the creases of the neck and axillae. Erythematous, denuded, moist areas were noted on the buttocks. Nikolsky's sign was positive. The remainder of the physical examination was negative.

Pemellin ointment was applied generously to the entire body three times daily and intramuscular pemellin, 50,000 units every three hours, was also employed. Phenobarbital was used as needed to prevent scratching and restlessness. As with the other patients, all clothes were removed from the infant's body, mineral oil was used to remove crusts, and a heat cradle was placed over the baby. Nutramigen and a high vitamin diet were employed. On the thirteenth day all medication was discontinued.

A few days after admission other erythematous areas began vesiculating and four days later the skin began exfoliating from these areas leaving a denuded, inflamed derma. At that time the skin of the face began assuming a normal appearance and by the thirteenth day the entire body appeared normal. The patient was discharged on the seventeenth day.

DISCUSSION

Probably all forms of exfoliative dermatitis are merely reactions of the body to systemic or local irritants. Such irritants may be classified under the headings of living and nonliving, the living irritants including pathogenic microorganisms and animal parasites and the nonliving including physical (trauma, electricity, pressure, light, roentgen rays, radium radiations, foreign bodies, heat, cold, etc.) and chemical (drugs, poisons, acids, alkalis, etc.) agents.

The diagnostic terminology applied to each individual case of exfoliative dermatitis is generally determined by the irritant or irritants involved plus the clinical course of the disease and not by the skin lesions alone for several separate disease entities may exhibit almost identical skin lesions.

Ritter's disease (dermatitis exfoliativa neonatorum, keratolysis neonatorum) will be fully discussed, with the thought in mind that Leiner's disease, Savill's disease, pemphigus neonatorum, acute epidermolysis of the newborn, impetigo of the newborn, and possibly drug or contact dermatitis of the newborn are probably merely variants of this same condition, since the clinical pictures are quite similar.

The etiological agent responsible for Ritter's disease remains obscure, most authors favoring an infectious origin (staphylococcus, streptococcus, virus, etc.) while a few favor a disturbance of the endocrine system. In all probability the infectious nature is merely the result of secondary invaders or contaminants. It is our belief that the causative factor may be any type of irritant, either systemic or topical.

The onset of the condition known as Ritter's disease may occur from the second day of life to the fifth week, the average occurring during the second week. It may be sporadic or epidemic in nature, depending on the causative irritant involved. The disease usually runs its course in a period of seven to ten days; however, severe cases may last a month or longer. Recovery is usually permanent although recurrences are not too uncommon, some developing years after the initial attack.

The skin rash itself has been described in all gradations of severity and type, hence we will discuss the picture as it may occur, keeping in mind that all or any part of this picture may exist. The rash is generally preceded by a fine desquamation of the skin, and begins with erythematous patches which enlarge and coalesce. These patches progress to the point of exfoliation, leaving thin or thick scales of epidermis covering the body and overlying a raw, red derma appearing not unlike a second-degree burn. The derma beneath the crusted, exfoliated epidermis is generally moist although it may be dry and inflamed. Vesicles and bullae with inflamed areolae may be present, the vesicles having a tendency to confluency and the bullae containing serous or purulent fluid. These lesions also rupture and desquamate as previously described. Crust-covered fissures at the mucocutaneous junctions are not uncommon. Islands of apparently normal skin, when gently rubbed or traumatized, exhibit the phenomenon of epidermolysis; i.e., the epidermis peels away revealing a raw, inflamed, usually edematous derma (also known as Nikolsky's sign). With the cessation of the scaling there is a gradual diminution and clearing of the erythema and re-epithelialization of the skin.

The rash usually begins on the lower part of the face, i.e., the cheeks, chin, and angles of the mouth, and spreads rapidly to the neck, arms, legs, and body. Exfoliation is generally evident within one to three days of the onset. The mucous membrane of the mouth, nose, and conjunctiva may be involved and there may be edema of the eyelids, lips, ears, and legs.

The temperature is usually below normal or within normal limits; however, an occasional patient may run a fever as high as 104° F. and chills may occur.

The majority of deaths due to Ritter's disease are the result of complications, hence the major part of the treatment should be directed toward the prophylaxis against complications. We attribute the survival of our four patients largely to the prophylactic use of parenteral and topical (ointment) penicillin, thus preventing the complications that are usually considered to be the causes of death.

The uncomplicated case generally presents few or no constitutional symptoms whereas the complicated case usually exhibits symptoms referable to the gastrointestinal tract, such as vomiting, diarrhea, marasmus, etc. Following

are complications of Ritter's disease, extracted from the literature, that are thought to decrease the infants' chances of survival: pneumonia, furuncles, abscesses, stomach and intestinal ulcers, secondary infections, gangrene, sepsis, septicemia, dehydration and anuria, hypothermia, toxemia, hypoproteinemia, lymphangitis, lymphadenitis, Waterhouse-Friderichsen syndrome and other endocrine disturbances.

Many forms of treatment have been employed. Among the topical forms are ointments of sulfonamides (sulfanilamide, sulfathiazole), ammoniated mercury, zinc oxide, tar, Ichthyol, cold cream and chrysarobin; oils such as olive and caron; powders as talcum, zinc oxide, starch, and zinc peroxide; solutions of potassium permanganate, tannic acid, methylene blue and physiologic sodium chloride; and tincture of benzoin. Breast feeding has been considered a must and oral medications have consisted of sulfapyridine, sulfathiazole, sulfadiazine, sulfanilamide and vitamins A, C, D, and B. Transfusions of whole blood, intramuscular injection of human serum or maternal blood, ultraviolet radiation, and small doses of roentgen radiation have been employed.

In view of the excellent results obtained with the four cases herein reported, it appears as though the most satisfactory form of therapy to date consists of general maintenance, warmth (heat eradle), no clothes, no baths, as little handling as possible, and intramuscular penicillin and penicillin ointment applied topically (so that the entire body is covered and moist at all times). It is suggested that these measures be employed for several days after complete recovery in order to avoid the possibility of a recurrence. Sulfonamides may be employed if deemed necessary. Any mode of therapy must be directed toward the prevention of complications.

SUMMARY

1. Four patients with Ritter's disease have been treated with topical and parenteral penicillin with 100 per cent recovery.

2. It is believed that the results obtained were due to the prevention of complications.

3. The etiology, diagnosis, complications, and treatment of Ritter's disease are briefly discussed.

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TWO UNUSUAL VASCULAR AND CARDIAC ANOMALIES

I. VASCULAR RING OF THE ESOPHAGUS AND TRACHEA WITH PATENT DUCTUS ARTERIOSUS ORIGIN OF THE LEFT SUBCLAVIAN AND CAROTID ARTERIES

II. PERSISTENT ATRIOVENTRICULAR COMMUNIS AND AORTIC DEXTROPOSITION WITH MONGOLISM

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ADDED interest in congenital vascular and cardiac anomalies has been aroused by recently developed methods for the surgical correction of some of these defects.^{1, 2} The basis for these new methods has developed over many years through studies of the etiology, incidence, and diagnosis of the heart anomalies. When the post-mortem findings are correlated with the clinical symptoms and signs, the diagnosis and treatment of similar cases in the future will be made easier. These two congenital anomalies are reported with this objective.

CASE 1.—This full-term, white, male infant was delivered at St. Luke's Hospital on March 2, 1948, in the service of Dr. J. E. Fitzgerald. Death occurred approximately thirty hours later.

History.—The mother was a 20-year-old gravida ii, para i, white woman. Her prenatal condition had been uneventful. She had gained twenty-six pounds in weight, and gave no history of having contracted any infectious or contagious diseases during pregnancy. She entered the hospital in active labor on March 2, 1948, at 5:30 A.M., and after one hour spontaneously delivered a full-term living male infant weighing 5 pounds, 14½ ounces. Respirations began at once and the cry was described as fair in quality. The infant had bilateral congenital absence of the lobule and the inferior portion of the helix of the ears, and the testicles were not palpable in the scrotal sac.

He was transferred to an oxygen-tent-crib in the nursery because of slightly labored respirations and excessive mucus exuding from the nasal passages. Frequent nasopharyngeal aspirations were necessary because of the copious quantities of mucus which continually accumulated and exuded from the nose and mouth. Cyanosis of the skin of the face, especially about the nose and mouth, appeared but improved markedly following the nasopharyngeal aspirations. Twelve hours after delivery an unsuccessful attempt was made to give water by mouth, and body fluids were maintained by subcutaneous injections of Ringer's lactate solution. On the second day after birth the rectal temperature was 100° F. A loud systolic murmur was heard over the entire precordium, the breath sounds in the left chest were decreased, the respirations were labored, mucus secretions in abundance continued to exude from the nose and mouth, and cyanosis of the skin of the face persisted despite the continuous administration of oxygen and frequent nasopharyngeal aspirations. Penicillin and Synkamin were given but he failed rapidly and expired approximately thirty hours after birth.

Excerpts from the necropsy protocol follow:

The body of this full-term, white male infant weighed 5 pounds, 14½ ounces, and had a crown-heel length of 47 cm., a crown-rump length of 34 cm., a congenital absence of the lobule and the inferior portion of the helix of the ears, and no palpable testes in the scrotal sac. When the chest structures were exposed several anomalies of the main cardiac vessels

From the Henry Baird Favill Laboratory, St. Luke's Hospital.

were observed (Figs. 1 to 4). These are listed as follows: (1) persistent aortic right arch and congenitally absent aortic left arch; (2) patent ductus arteriosus from which ascended the left common carotid artery and the left subclavian artery; (3) dilatation of the pulmonary conus; (4) congenitally absent innominate artery; (5) persistent left superior vena cava, which emptied into the right auricle of the heart, and communicated with the right superior vena cava through the left innominate vein.

The aortic right arch arose at the base of the heart, ascended, and curved in front of the right main bronchus. The arch then extended posteriorly behind the esophagus and trachea and emerged to the left and posterolateral side of these structures. At this level the aortic arch was joined by the ductus arteriosus and thus formed a vascular ring about the trachea and esophagus. The left common carotid artery and the left subclavian artery arose from the ductus arteriosus. After the aortic arch had anastomosed with the ductus arteriosus, the aorta descended as usual on the left side.

The myocardium of the heart was dark red-brown, fibrillar tissue. No unusual changes were in the right and left lungs, main bronchi, or trachea. The lining of the urinary bladder was gray and the lumen was markedly dilated. The urethra and urethral orifices were patent. The prostate gland was 1 by 1.2 by 0.6 cm. and surfaces made by cutting were gray, fibrillar tissue. The verumontanum was enlarged to 0.5 by 0.3 by 0.4 cm., and appeared partially to obstruct the urethral meatus. No other significant changes were observed on gross examination of the remaining tissues of the body.

Histologic examination of the tissues stained routinely with eosin and hematoxylin revealed: hyperemia and moderate atelectasis of the lungs; hyperemia and fatty changes of the liver; hyperemia of the spleen; and extramedullary hematopoiesis of the liver and spleen.

DISCUSSION

In reviewing the development and modification of the aortic arches and the normal embryology of the vascular system, Congdon's³ excellent monogram and various embryologic texts^{4, 5} have been consulted. In the human embryo, six pairs of aortic arches develop, all of which are not present at any one time during fetal development. The period of development of the aortic arches extends throughout the fourth week, and their transformation occupies mainly the fifth to seventh weeks. According to Arey, the characteristic changes of this region are brought about by the loss or interruption of some arches and segments of the aorta.

In the second week of embryonic life, the heart is a single chamber, on each side of which is a ventral aorta, an aortic arch, and a dorsal aorta. Toward the end of the fourth week the paired ventral aortas unite to form the bulbus arteriosus and the dorsal aortas combine to form a common descending aorta. Before fusion of the two dorsal segments, each gives off approximately thirty dorsal branches. After the fusion of the dorsal aortas these dorsal branches become the posterior paired intersegmental arteries.

The development of the six pairs of aortic arches occurs by the fusion of the dorsally growing branches from the bulbus arteriosus with ventrally growing branches from the dorsal aortas.

Normally the external carotid arteries represent the surviving elements of the paired ventral aortas. The internal carotid arteries are derived from the third arches and the persisting cephalic portions of the original paired dorsal aortas. The portions of the dorsal aortas which lie between the third and fourth arches disappear.

The right ventral aorta becomes the right intercostal artery. The subclavian artery is derived from the fourth right intercostal space. The right dorsal aorta and the sixth intercostal space. The subclavian arteries are usually incorporated in the subclavian space.

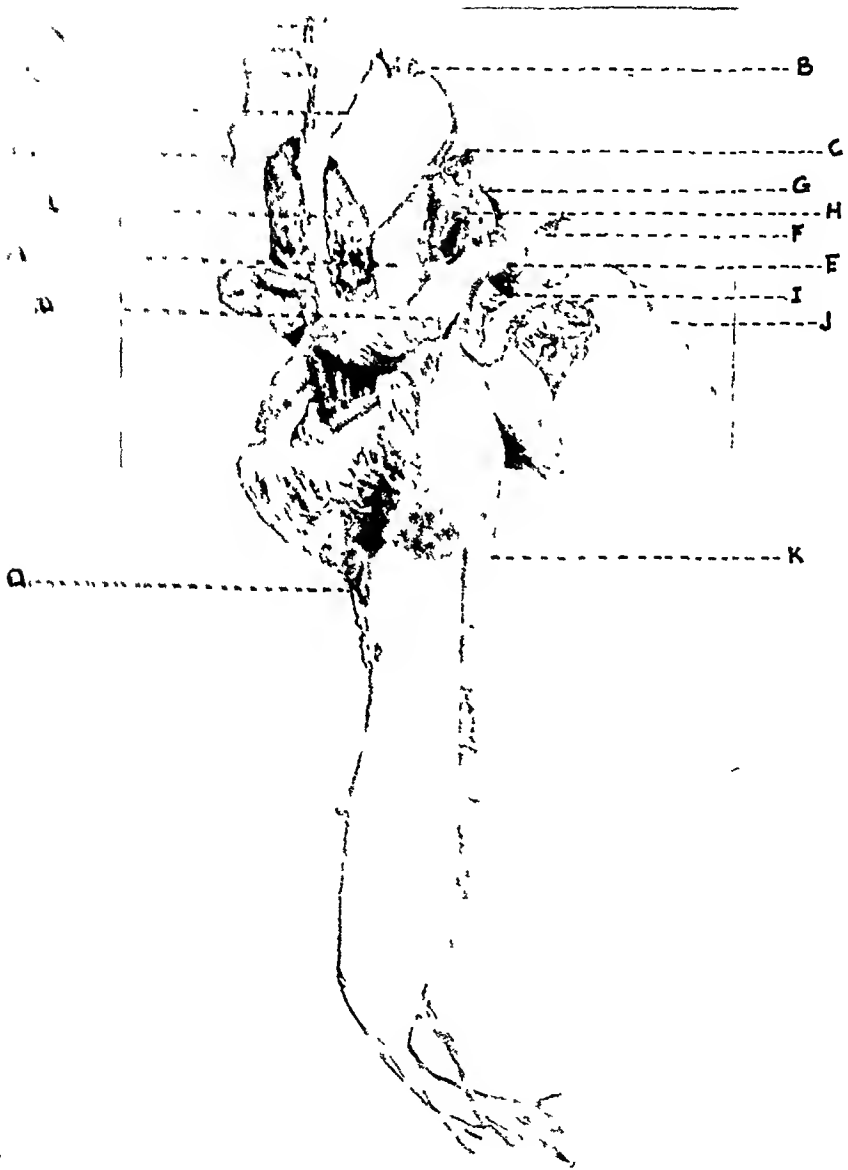


Diagram of the thoracic cavity illustrating the right arch. A, right ventricle; B, right atrium; C, right ventricle; D, dilated pulmonary conus; E, dilated pulmonary conus; F, dilated pulmonary conus; G, dilated pulmonary conus; H, trachea; I, left ventricle; J, left atrium; K, descending aorta; L, right superior vena cava; M, right inferior vena cava; N, right innominate vein; O, left superior vena cava; P, left inferior vena cava.

On the left, the fourth left arch becomes the definitive aortic arch which continues caudally as the descending aorta.

The pulmonary arteries arise from the proximal portion of the sixth arches. Only on the left does the distal half of the sixth arch persist, and here it becomes the ductus arteriosus. When the bulbus arteriosus divides sagittally, the pulmonary and aortic systems become separate.

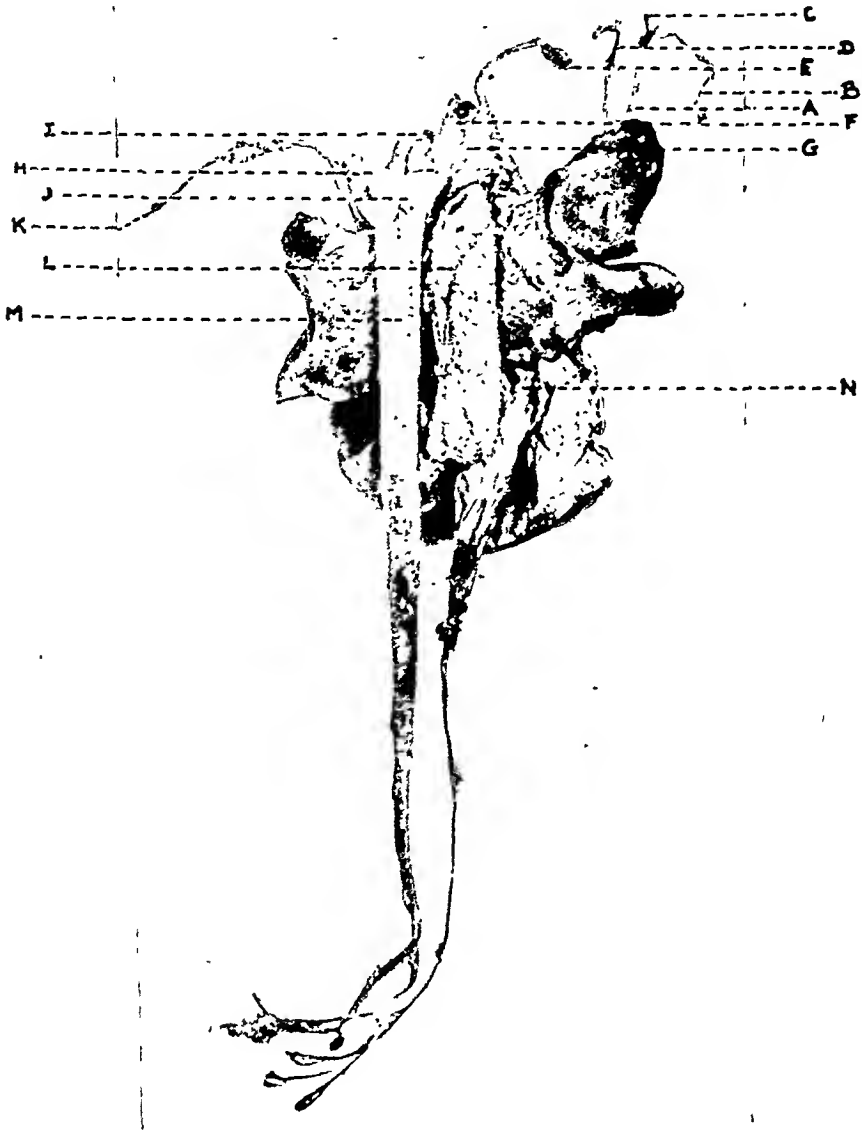


Fig. 2.—Dorsal view of the heart and vascular tree illustrating A, right innominate vein; B, right subclavian vein; C, right jugular vein; D, left innominate vein; E, right subclavian artery; F, right common carotid artery; G, aortic right arch; H, left common carotid artery; I, left subclavian artery; J, anastomosis of the ductus arteriosus with the aortic right arch; K, persistent left superior vena cava; L, esophagus; M, descending aorta; N, inferior vena cava.

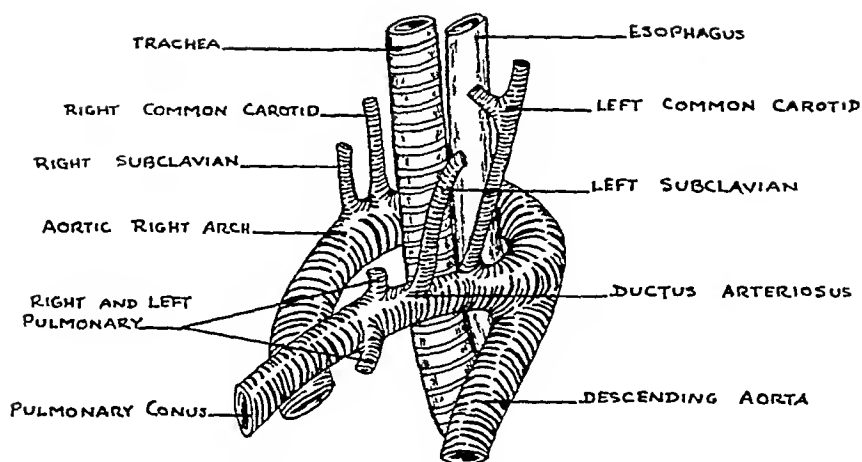


FIG 3—Left lateral view illustrating the congenital anomalies of the aortic system

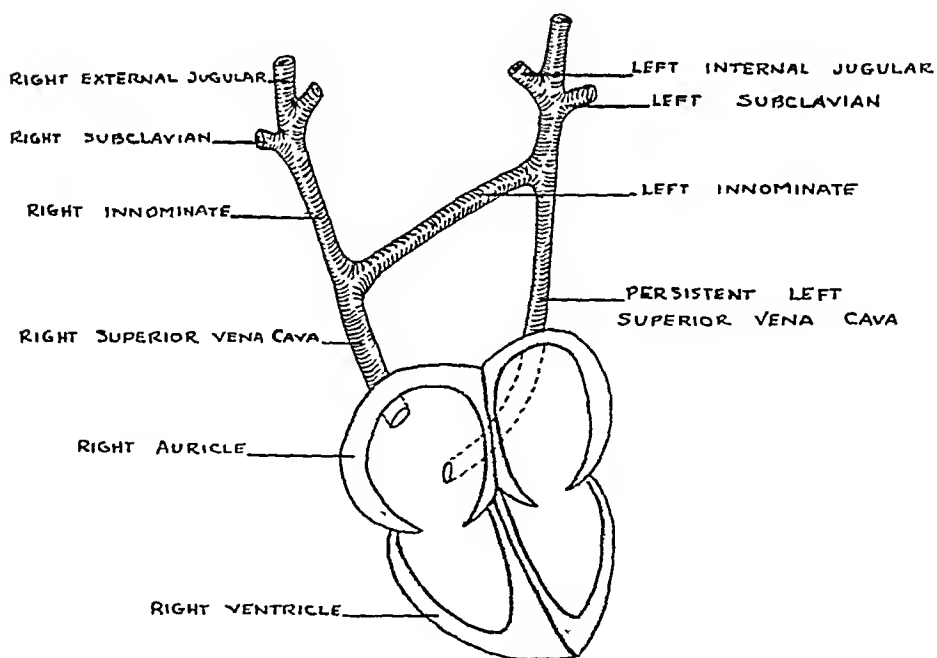


FIG 4—Ventral view illustrating the congenital anomaly of the venous system

Since the first of the vascular anomalies described in this report (Case 1) concerns the venous system, a brief résumé of the formation of the superior vena cava follows: The paired anterior cardinal veins pass caudally from the jugular foramen to Cuvier's ducts on each side as the internal jugular veins. In the neck region an asymmetrical organization of the venous system is accomplished through the development of the left innominate vein. This vein arises from the left internal jugular vein and passes obliquely and to the right to fuse with the right internal jugular vein. The segment of the left internal jugular vein which remains between the innominate bifurcation and the left duct of Cuvier becomes obliterated; however, it persists as the ligament of Marshall. That portion of the right internal jugular vein caudal to the junction of the left innominate vein with the right duct of Cuvier becomes the definitive superior vena cava.

To explain the congenital vascular anomalies reported in this child, probably some developmental defect occurred during the fourth to seventh week of intrauterine life, or at about the time the vascular tree was in the process of development (Figs. 3 and 4). The defective growth caused changes as follows (1) The fourth aortic left arch (which normally becomes the definitive aorta) atrophied and the aortic right arch persisted as the definitive aorta. (2) The ductus arteriosus drew the aortic right arch sharply to the left (posterior to the esophagus and trachea), fused with it, and thus produced a vascular ring. Following the anastomosis of the aortic right arch with the ductus arteriosus, the aorta descended in the usual manner on the left side as the descending aorta. (3) Due to the absence of the aortic left arch, the left common carotid artery and the left subclavian artery grew caudally and laterally to form an anastomosis with the ductus arteriosus. (4) It is difficult to explain the congenital absence of the innominate artery; however, Taussig⁶ states this is not an unusual finding in the presence of a persistent aortic right arch. (5) Because that portion of the left internal jugular vein caudal to the junction of the left innominate vein and cranial to the left duct of Cuvier remained patent, there existed a left superior vena cava, which like its analogue on the right, emptied into the right auricle of the heart.

COMMENT

The clinical symptoms of cyanosis, labored respiration, and copious secretions of mucus from the nasopharynx probably resulted from compression of the trachea and esophagus by the vascular ring (aortic right arch and the ductus arteriosus). Sweet and associates⁷ reported a vascular ring (aortic right and left arch) in a 3½-month-old infant which caused coughing, wheezy respirations, and feeding problems. In the case herein discussed (Fig. 3) it is deemed problematic whether or not ligation of the ductus arteriosus distal to the bifurcation of the pulmonary arteries would have been justified had the diagnosis been made ante mortem. One should consider that with ligation of the ductus arteriosus distal to the bifurcation of the left common carotid and left subclavian artery, the blood supply to the left side of the face, neck, and arm would have been venous.

Again, the presence of one congenital anomaly suggests the possibility of others.

CASE 2.—Clinical Brief. This 9-month-old male infant was admitted to St. Luke's Hospital in the service of Dr. S. C. Henn in critical condition on March 7, 1948, and died eight and one-half hours later. His mother was a primipara Negress in good general health without significant past or family history, but with a loud systolic cardiac murmur. Her blood Kahn test was negative. She had an uneventful pregnancy with a low forceps delivery, at term, of the 7 pound, 2½ ounce male infant. Despite a lusty cry and good color, he was unable to nurse and was placed on formula feeding. Physical examination revealed complete muscular flaccidity, mongoloid eyes, possible congenital cataracts, hypermobility of wrists, hips, ankles, and feet, normal little fingers, and no heart murmurs.

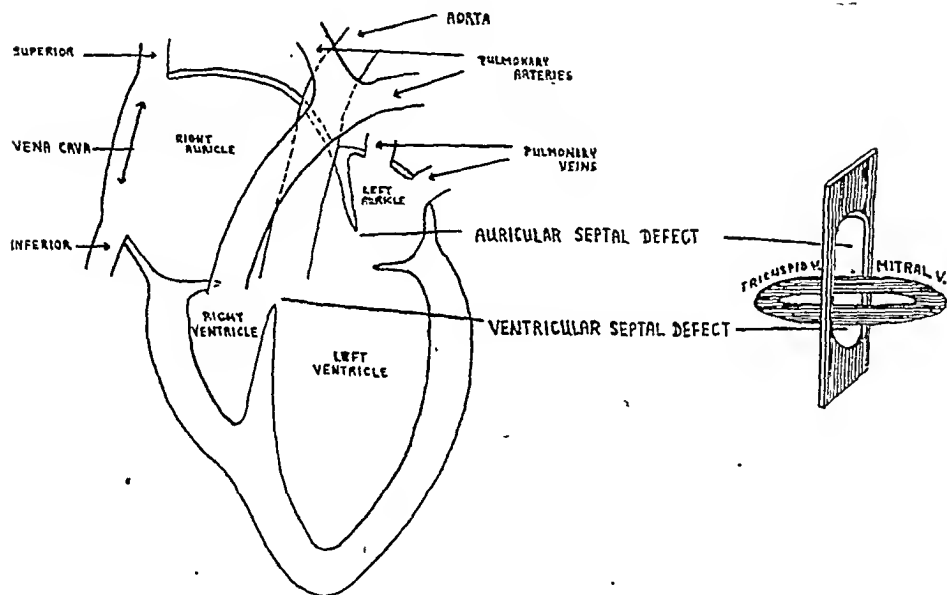


Fig. 5.—Diagram of the heart in Case 2 showing the persistent atrioventricular communis, underdeveloped right ventricle and left auricle, enlarged left ventricle and right auricle, and dextroposition of the aorta.

During the subsequent months he gained weight slowly, and at 5 months of age was circumcised. Three weeks before death he began to cough persistently and had a fever. A loud, systolic murmur then was heard over the entire precordium for the first time. On the day before admission to the hospital the mother noticed that the baby did not eat well and that his cough was worse. By the next morning when he was brought to the hospital, he had marked retraction of the soft muscles of the thorax with inspiration because of dyspnea. His rectal temperature was 105.8° F., his respiratory rate was 80, and his pulse was too rapid to be counted. The lungs had moist râles and a left pleural friction rub. The left lobe of the liver was palpable at the umbilicus. Subcutaneous fluids, penicillin, sulfadiazine, aspirin, and oxygen were started and the baby's rectal temperature dropped to 102° F. two hours later and the heart rate was reduced. With the latter a gallop rhythm was evident. However, his condition did not improve and he died a short time later. The clinical diagnosis was congenital heart disease with chronic heart failure, bronchopneumonia, and Mongolian idiocy.



Fig 6—Posterior view of the heart in Case 2 illustrating A, the small size of the right ventricle, B, the interventricular septum, C, the interventricular septal defect, D, the right part of the anterior valve leaflet, E, the right lateral valve leaflet, and F, the space under the anterior leaflet.

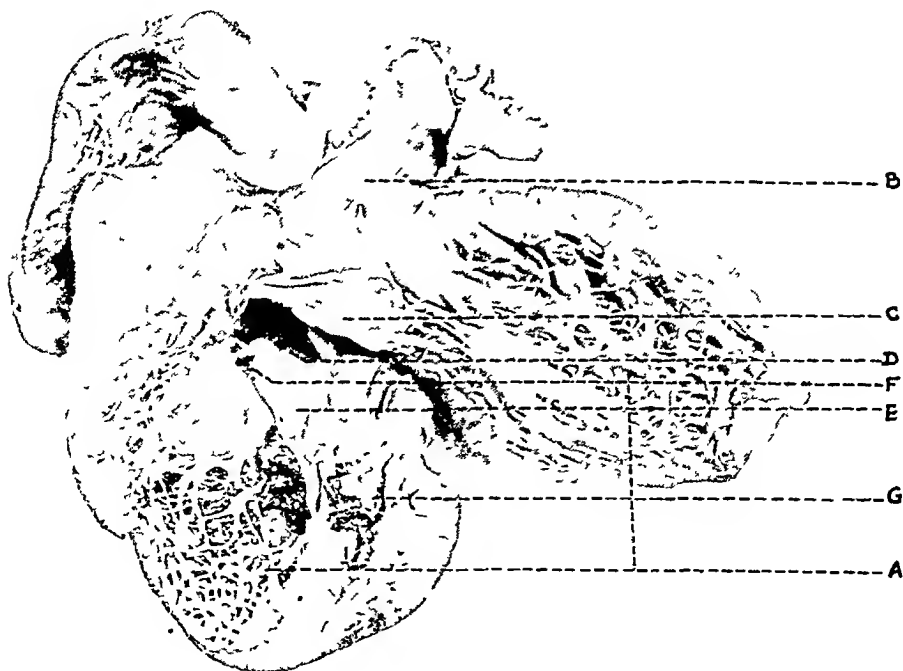


Fig 7—Left anterior view in Case 2 of A, the opened enlarged left ventricle, B, the dextroposed aorta, C, the left part of the anterior valve cusp, D, the interventricular septal defect, E, the posterior valve cusp, F, the space under the posterior valve cusp and G, the left lateral valve cusp.

Necropsy.—The body of this well-nourished Negro male infant weighed 5,450 Gm., was 65 cm. long (normal for this age, 8,000 Gm. and 67 cm.), had mongoloid features, and had an anterior fontanelle 2 by 2 cm. There were moderate ascites, bilateral hydrothorax, and hydropericardium. Focal regions of bronchopneumonia, hyperemia, and edema were present in the lungs. The liver had a chronic passive hyperemia. The greatly enlarged, abnormally shaped heart weighed 85 Gm. (normal for this age, 37 Gm.). Most of the enlargement was in the dilated right auricle and left ventricle because the left auricle and right ventricle were small by comparison. There were no venous anomalies. A probe introduced into the heart through the pulmonic artery passed only into the right ventricle, but when introduced through the aorta passed easily into either the left or right ventricle (see Fig. 5).

The left and right ventricular walls were each one centimeter thick. The length of the left ventricle from the attachment of the atrioventricular valve ring to the apex was 5.4 cm. in contrast to a corresponding measurement in the right ventricle of 2.5 cm. (Figs. 6 and 7). There were thin membranous eustachian and thebesian valves.

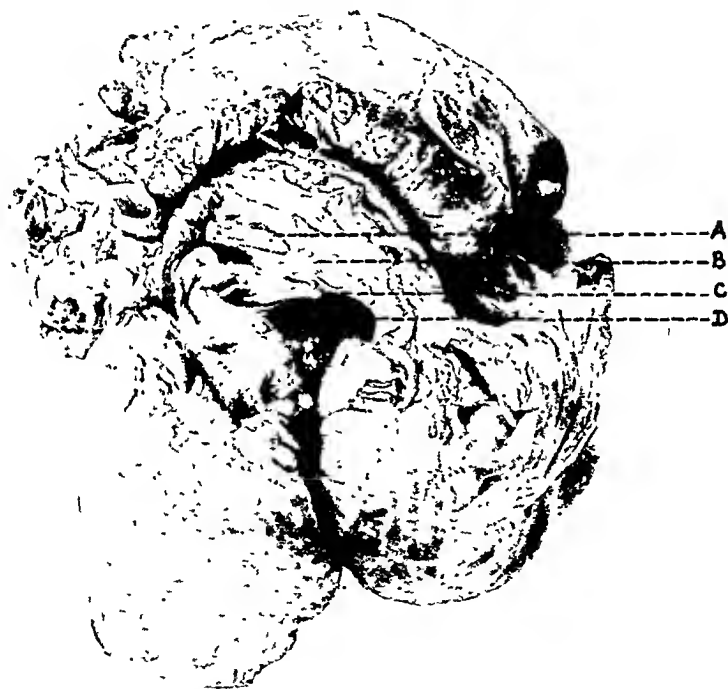


Fig. 8.—Photograph looking down into the left auricle in Case 2 illustrating A, the patent foramen ovale with a probe through it; B, the interauricular septum; C, the free edge of the interauricular septal defect and D, the left atrioventricular orifice.

The interauricular septum above was complete although the fossa ovalis was patent through an oblique channel 0.3 cm. in diameter (see Fig. 8). The septum deviated markedly to the left inferiorly and was incomplete through an opening 1.3 cm. anteroposteriorly and 0.5 cm. above the common atrioventricular ring. Its crescentic free border formed the right part of an oval left atrioventricular ostium 1.5 cm. in diameter (Fig. 8). The septum primum appeared to be well developed, but the septum secundum was not well formed, especially in the anterior portion.

The interventricular septum was complete in its lower part, but above it was incomplete. Its free margin was 1.2 cm. to the right of the lower free border of the interauricular

septum. The free border of this septal defect arched downward from the attachments of the common atrioventricular valve cusps 1 cm. and was 1.3 cm. in its anteroposterior measurement to form an opening through which the ventricles communicated freely (Fig. 7).

There was a single large atrioventricular orifice. Its right half functioned as the right atrioventricular orifice, but its left half or one-fourth with the interauricular septal defect functioned as the left atrioventricular orifice as previously described. The large orifice was guarded by a valve composed of four segments, one large anterior segment partially divided at the interventricular septum so that the right half corresponded to the anterior leaflet of the tricuspid valve (Fig. 6, *D*). At the right and left ends of the orifice were small leaflets somewhat corresponding to the posterior cusps of the usual valves (Figs. 6, *L*, and 7, *G*). Posteriorly over the free edge of the septal defect more on the right than on the left was another large, somewhat central leaflet probably representing the medial cusp of the tricuspid valve (Figs. 7, *L*, and 9, *E*). It was attached closely to the free margin of the underlying septum by a group of short chordae tendinae, thus leaving little communication between the ventricles in this location (Fig. 7, *F*). The defect under the anterior segment was deep with three chordae tendinae about one centimeter long (Fig. 6, *F*).



Fig. 9.—Photograph of the formalin fixed heart in Case 2 looking down into the right auricle illustrating *A*, the right part of the anterior valve leaflet, *B*, the interauricular septum; *C*, the right lateral valve leaflet, *D*, the displacement of the interventricular septum to the right; and *E*, the posterior valve leaflet.

The orifice of the aorta which was located to the right straddling the interventricular septal defect was in front of the anterior leaflet of the atrioventricular valve. Under slight tension the circumference of the aortic valve ring was 3.4 cm. and its leaflets were fenestrated near the commissures (Fig. 7). The orifice of the pulmonic artery was pushed to the right by the dextroposition of the aorta. Its leaflets also were fenestrated, and the circumference of the pulmonic ring was 3.1 cm.

The vessels leaving the heart were normal in size and without anomalies. The ductus arteriosus was closed. There were no other significant gross findings.

Histologically, sections of tissues stained with hematoxylin and eosin revealed marked chronic passive hyperemia of the lungs, liver, and spleen, and slight bronchopneumonia.

DISCUSSION

Congenital cardiac terata are reported to be caused by numerous factors, as hereditary influences, dysontogenesis, various infections of the mother such as syphilis and rubella early in pregnancy, poor prenatal diet, maternal hormonal and metabolic imbalances, and many others. In this case, as in most, there is no evident material or fetal etiology. About one-half of the reported cases of the cardiac malformation have occurred with Mongolian idiocy.⁸ This would seem to indicate that the phase of fetal development during which this or a similar heart anomaly occurs is approximately at the same phase during which mongolism occurs. Consequently, an arrest of the forming fetus at this time results in both anomalous conditions.⁶ Because numerous cases of normal offspring of Mongolian idiots have been reported, most authorities do not believe that the condition is due to hereditary factors.³ By analogy, the same reasoning applies to the cardiac anomaly here discussed. Furthermore, in known cases of insult to the developing embryo from a rubella infection in the mother early in pregnancy, similar heart malformations have resulted.¹⁰

Because embryologists are not entirely agreed as to the method of fusion of these four heart structures—the endocardial cushions, interauricular, interventricular, and bulbar septums—an exact explanation of the mechanism of formation of septal defects associated with a common atrioventricular orifice is not possible. However, following the ideas advanced by Arey⁵ on development of the normal human heart, the anterior and posterior endocardial cushions fuse in the midline in a figure-of-eight fashion dividing the common atrioventricular canal into a right and a left channel. Meanwhile, the septum primum, growing down from above, attaches to the already merged endocardial cushions by the end of the sixth week of embryo (12 mm.) formation. At the end of seven weeks (17 mm.) the septum membranaceum has closed by proliferation of tissue from the endocardial cushions, completing formation of the interventricular septum which has been growing up from below.

Therefore, in the case presented in this paper it appears that late in the fifth or early in the sixth week some growth defect occurred, preventing formation and fusion of the anterior and posterior endocardial cushions so that there was no place to which the descending septum primum and ascending interventricular septum could attach.

The small size of the right ventricle and dextroposition of the aorta can be explained on the basis of Spitzer's theory of incomplete rotation and torsion of the developing fetal heart.¹¹ Normally, during the fifth and sixth weeks of embryo formation the simple tubelike heart of preceding weeks grows faster than its pericardial sac, forming a spiralled S shape. The chief primary flexure is to the right, and by means of it the bulbus and ventricle become a U-shaped loop (the right limb or bulbus part forms the right ventricle and the left limb

forms the left ventricle). The origin of the aorta and pulmonary arteries is brought about through longitudinal ridges developing in the superior bulbus and fusing to create a septum. Apparently in the case under discussion the right limb of the loop failed to descend caudal enough or rotate to the left enough, resulting in underdevelopment of the right ventricle and dextroposition of the aorta.

The marked dilation of the right auricle is due to the displacement of the interauricular septum to the left, thereby decreasing the size of the left auricle and increasing the size of the right. Also, the ventricular pressure was transmitted to the right auricle through the markedly incompetent common atrio-ventricular valve, thereby leading to the dilatation of the thin auricular musculature.

Comment.—In this case, as in the first, some defect occurred during the fifth or sixth week of fetal growth, resulting in an incomplete torsion of the heart, failure of growth and fusion of the endocardial cushions, and Mongolian idiocy.

SUMMARY

Two cases of congenital heart disease are presented: one showed an aortic right arch and left descending aorta, a persistent left superior vena cava, and anomalous origin of the left common carotid and left subclavian arteries from the ductus arteriosus; the other showed an atrioventricular communis, dextroposition of the aorta, underdevelopment of the right ventricle and left auricle, and enlargement of the right auricle and left ventricle.

Such congenital vascular and cardiac anomalies are frequently associated with other anomalies. In the first case, the ear lobes were absent and the testicles were undescended. In the second case, the child was a Mongolian idiot.

In reviewing the literature, we were unable to find any similar descriptions of the anomalies reported above. Due to the important role which surgery now holds in the correction of many similar congenital vascular diseases, these two cases are presented.

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RADIATION THERAPY FOR WILMS' TUMOR OF THE KIDNEY

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WILMS' tumor may be treated surgically, radiologically, or by a combination of both therapies. A more detailed study of these methods shows that the management of the patients actually falls into five classes, each of which has its worthy exponents. The classes are as follows:

1. *Operation Alone:* - The surgical treatment consists of nephrectomy through the lumbar route or transperitoneally. Ladd^{1, 2} is the outstanding advocate for this method. All surgeons recognize, however, that this procedure is of no avail in the presence of pulmonary or other metastases. As frequently happens, the tumor mass may be too huge for removal, when first seen, although Ladd has been successful in removing tremendous growths by the transperitoneal approach.

2. *Operation and Postoperative Irradiation:* This combined method was probably the treatment of choice until recently. The postoperative irradiation destroys the embryonic malignant cells which have been inadvertently disseminated or left behind during surgical removal. Among others, Nesbit,³ Hazzard,⁴ Weisel,⁵ and Priestley⁶ advocated this method, although the latter now states that the combined method of pre- and postoperative irradiation may offer the best possibilities.

3. *Preoperative Irradiation and Operation:* For those who find the growth too massive for removal when first observed, a course of high voltage roentgen treatments is administered. The tumor is thus sufficiently reduced in size so as to permit surgical extirpation. An inoperable mass is rendered operable. Randall,⁷ Kerr,⁸ and others support this method of approach. The pre-nephrectomy irradiation not only shrinks the huge mass but also minimizes local and widespread dissemination of the embryonic tumor cells by sealing off the blood vessels and the lymphatics.

4. *Preoperative and Postoperative Irradiation:* This is the treatment of choice today, being advocated by a majority of the workers in this field. Among its advocates may be mentioned Adams,⁹ Campbell,¹⁰ Rowe,¹¹ Priestley,¹² Mertz,¹³ Higgins,¹⁴ Kretschmer¹⁵ and others. The full advantages of both surgery and irradiation are embodied in this method.

5. *Irradiation Alone:* Radiation therapy alone is considered by some workers as the treatment of choice. They regard the growth as too dangerous to remove surgically because of its tendency to metastasize. Being highly malignant, Wilms' tumors are extremely radiosensitive and are considered, therefore, to be a radiation problem. Among the supporters of treatment by irradiation alone may be mentioned Dean,¹⁶ Barringer¹⁷ and others. It is well to mention here that inasmuch as the entire treatment is dependent upon irradiation without surgery, the cycle of roentgen treatments should be intensive. It is gen-

erally conceded that irradiation alone is the treatment of choice in the presence of metastasis, as nephrectomy is contraindicated (Fig. 1). Roentgen therapy under such circumstances is administered for palliation only. It is therefore wise to take roentgenograms of the chest and skeletal system to rule out the presence of metastases when surgery is contemplated (a radiologic procedure which should be routine for all patients when first seen).



Fig. 1.—H. S., a 9-year-old girl, whose symptoms were: a large mass in right abdomen, loss of weight, tiredness and cough with one episode of hemoptysis of two weeks' duration. Bilateral pyelography showed a tremendous right renal tumor. She received x-ray therapy alone with marked reduction in size of the mass. Operation was contraindicated because of extensive lung metastases (see Fig. 2).

Radiation Technique.—The technical factors involved in the roentgen treatment of Wilms' tumors depend on the age and general condition of the patient and the size of the tumor. One should also take into account whether the series of treatments is merely for palliation alone (as in cases with metastases) or whether nephrectomy is contemplated. Usually three portals of entry are employed over the mass, an anterior, a lateral, and a posterior field. Occasionally in a massive lesion six portals are preferable in place of three large areas. The advantages of multiple small portals are, first, a greater total dose can be given without permanent damage to the skin; second, more accurate cross-firing of the tumor may be thus obtained, and third, there is less likelihood of radiation sickness when small portals are used. The tissues surrounding the tumor mass should be included in the irradiated field.

The total dosage varies from 3,600 to 6,000 r. The treatments are given daily, one portal being treated when only three are mapped out over the mass,

A.



B.

Fig. 2.—Same patient as in Fig. 1. *A*, Extensive pulmonary metastases before roentgen therapy. *B*, Pronounced improvement two months after treatments. Child died six months after initial visit. Post-mortem examination revealed a Wilms' tumor of the right kidney with vascular invasion involving the pulmonary artery and the left ventricle and with metastases to the liver, lungs, retroperitoneum, and genital tract.

or two portals are given daily when six of smaller size are employed. No more than a total of 200 r in either case is given daily with the following technical factors: KVP 200; T.S.D. 50 cm.; portals 6 by 8 cm. or 10 by 10 cm.; H.V.L. 1.8 mm. of cu. The cycle of treatments is usually completed in from three to five weeks. In order that the full effects of the irradiation are obtained, operation, if it is to be performed, should be delayed for from four to six weeks after the completion of the course of roentgen treatments. After such a waiting period there is no detrimental effect to prevent prompt healing of the surgical wound.

In younger subjects (2 to 4 years of age), the total dosage should be slightly less than in a child of 8 or 9 years. A malnourished baby is usually less able to tolerate a full course than an older, well-nourished child.

The treatment of metastatic lesions is palliative and is similar to the roentgen treatment for the primary lesion. In the chest, irradiation is directed through three or more small portals for each lung and no more than 200 r is delivered daily for a total of 800 to 1,200 r for each field. The radiosensitivity of the tumor is evident by the rapid initial improvement, which, however, is short-lived (Fig. 2).

ANALYSIS OF CASES

From 1930 to 1947, seventeen patients with Wilms' tumor were treated. The youngest was 3 months of age, the oldest 10 years. There were ten male and seven female patients in the group. In all of the patients the duration of symptoms was less than six weeks. All of these children are dead, the longest survival being fourteen months. The average survival among the seventeen cases was six and one-half months.

Four patients received pre- and postoperative x-ray therapy, with an average survival of six and one-half months. Although this survival rate is the same as for the entire group of cases, it must be borne in mind that these four patients had the largest tumors which prompted their referral by the surgeon for preoperative irradiation.

Five patients were treated without surgical intervention because of demonstrable metastasis. The average survival of these patients who received roentgen therapy alone was only four and one-half months, even though both the tumor mass and the metastatic foci (lungs) were adequately irradiated. These patients presented a hopeless outlook at the initial examination.

Eight patients received only postoperative roentgen treatments with a survival of eight and one-half months. In evaluating this longer survival rate, one must take into account the fact that they represented the more favorable cases, being operable both from the standpoint of size of the neoplastic mass and of freedom of distant metastases.

CONCLUSIONS

From this inadequate series it is unwarranted to draw any accurate conclusions. It is evident, however, that the present management for this malady is deplorable. Although an occasional survival is reported in the literature, the mortality is near 100 per cent. With our present-day armamentaria little improvement can be expected. Yet every effort should be made to salvage as many

as possible from what seems to be an inevitable fate. Frequent periodic examinations of all infants including careful palpation of both kidneys should be a routine matter. In this way it may be possible to recognize these cases at an earlier stage. There is an imperative need for closer cooperation between the surgeon, radiologist and pediatrician or family doctor. From our present knowledge an adequate course of pre- and postoperative irradiation to the tumor bed offers the best possibilities.

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A NOTE ON METHEMOGLOBINEMIA AND HEINZ BODY FORMATION IN CATS FED COMMERCIAL CRAYONS

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CLINICAL reports have appeared recently concerning intoxication from ingestion of wax crayons.¹⁻³ Infants after eating red, orange, or yellow crayons developed cyanosis, methemoglobinemia, and other manifestations of poisoning by aromatic amines. There seemed to be a need for investigating this problem in experimental animals and consequently the studies reported here were undertaken in which crayons were administered to cats.

PROCEDURE

Test crayons bearing labels of commonly used brands were obtained on the open market. Healthy cats were used which weighed 2.5 to 5.5 kg. and had become well acclimatized to the laboratory environment. In the first group of tests, crayons dissolved in corn oil were fed by stomach tube. Later tests consisted of feeding crayons incorporated in fish, or the regular ground meat diet, to fasted animals. Methemoglobin (MHb) and total hemoglobin (Hb) were measured in blood samples obtained by venipuncture from the saphenous vein employing the method of Andrews and Horecker.⁴ Heinz bodies were looked for in methyl violet-stained blood smears.⁵

RESULTS

Results of tube-feeding crayon in 25 to 50 c.c. of corn oil are shown in Table I. No increase in blood MHb level was observed. The normal range of MHb concentration in cat blood as judged from examination of one or more blood samples from sixty cats (other than those used in this work) can be said to be between 0.0 and 0.9 Gm. per cent MHb. Heinz bodies did not appear in the blood smear twenty-four or forty-eight hours after intubation, but a lipemia-like turbidity was noted in the sera for several hours. There was no objective evidence that the cats were injured in any way by the test.

TABLE I. EFFECT OF FEEDING CRAYONS IN CORN OIL BY STOMACH TUBE ON BLOOD MHb

CAT	GM. OF CRAYON ADMINIS- TERED	COLOR OF CRAYON	GM. MHb PER 100 ML. BLOOD ACCORDING TO TIME IN HOURS AFTER INTUBATION				
			0	3	4 $\frac{1}{4}$	6 $\frac{2}{3}$	24
A	6.7	Red* and Blue	0.2	0.2	0.3	0.3	0.3
B	5.9	Yellow	0.2	0.2	0.1	0.0	0.0
C	4.1	Red* and Blue	0.1	0.4	0.2	0.0	0.4
D	4.8	Red* and Blue	0.4	0.4	0.3	0.0	0.9
E	4.5	Red* and Blue	0.6	0.3	0.0	0.0	0.4
F	4.1	Yellow	0.1	0.0	0.3	0.0	0.3

*In equal proportions.

From the Laboratory of Physical Biology, National Institutes of Health.

TABLE II. METHEMOGLOBINEMIA AFTER INGESTION OF CRAYON IN THE DIET

EXPT. MENT	CAT	GM. OF CRAYON EATEN	COLOR OF CRAYON	GM. MHB PER 100 ML. OF BLOOD ACCORDING TO TIME IN HOURS AFTER OFFERING CRAYON MEAT MIXTURE										PER CENT ERYTHROCYTES CONTAINING HEINZ BODIES 24 HR. AFTER EXPOSURE			
				0	4	5	7	8	24	26	30	48	72				
				0.7	0.5	0.1			0.7								
1	1	11.9	Orange	0.4	0.1	0.3			0.0								
	2	11.3	Brown	0.2	0.0	0.3			0.7								
	3	14.5	Red														
	1-A	11.1	Red				2.7	1.7	2.1			0.6	0.5				
	2-A	10.4	Blue					0.7									
	3-A	14.3	Green				0.0	0.0	0.0								
	1-B	10.7	Red	0.0	0.0	0.1			0.1								
	2-B	16.1	Yellow	0.0	0.7	0.7			0.4								
	3-B	16.1	Purple	0.2	0.2	0.0			0.4								
	1-A	10.7	Red	0.9	0.4				0.7								
2	1	16.1	Orange	0.2	0.6	0.1			0.6								
	5	8.6	Orange	0.2	0.2	0.1			0.3								
	6	8.6	Red-Orange	0.1	0.0	0.4			1.6	1.5	2.1	1.2	0.3				
	7	8.6	Yellow	0.4					0.6	0.1		0.1					
	8	8.6	Green	0.4					0.3	0.7		0.0					
	9	8.6	Red	0.4					0.2	0.0		0.7					
	10	8.6	Red and Red-Orange	0.3					0.2	0.4		0.4					
	11	8.6	Orange and Red-Orange	0.2					0.2	0.0		0.2					
	1-C	8.0	Orange	0.1			0.0		0.0							1	
	1-A	8.0	Red	0.2			0.2		0.3							11	
3	2-C	2.9	Yellow	0.1			0.7									6	
	3-C	8.0	Red	0.2			1.6		1.8			0.1				98	
	4-B	15.0	Yellow	0.1			0.4		0.0							3	

Findings obtained in three experiments in which crayon was offered in the diet to fasted cats are presented in Table II. In three of the twenty-three exposures a moderate and prolonged methemoglobinemia developed with about 20 per cent of the pigment oxidized at the peak of the curve. The duration of the methemoglobinemia is comparable to that reported in human beings. Numerous large Heinz hodies were observed in the twenty-four- and forty-eight-hour blood smears of the positive cats in the first and second tests. Heinz body counts in the third experiment revealed a high percentage of these bodies only in the cat with methemoglobinemia. Because the proffered crayon-meat mixture was eaten after a variable and sometimes undetermined delay, the time intervals in the table do not relate to time when exposure to crayon began.

It is noteworthy that none of these animals presented any objective external manifestation of intoxication other than perhaps a slight apathy during methemoglobinemia.

DISCUSSION

From the data presented it is apparent that methemoglobinemia and Heinz body formation occur in a small percentage of cats fed commercial crayons. The results are more striking if only animals fed red or red-orange crayons are considered, in which group, one-third of the exposures resulted in MHB and Heinz body formation. No conclusion can be drawn from these results regarding poisoning in human beings. Relatively very large doses were given without evidence of serious intoxication other than the methemoglobinemia which per se is innocuous. Cats, it should be recalled, are probably the most susceptible species to methemoglobinemia. Possibly, however, the response of cats to oral crayon might prove useful in establishing, with further studies, the mechanism whereby crayons are toxic after ingestion by infants. A means is available perhaps to test the two postulates—individual idiosyncrasy vs. toxic contamination of the red dye. The latter point of view agrees better with the finding that the reaction was inconstant in one of our animals.

SUMMARY

Methemoglobin and Heinz body formation were observed in a small percentage of cats fed wax crayon in their diet.

The authors are indebted to Mr. E. C. Thompson for the Heinz body determinations.

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A NOTE ON POISONING DUE TO INGESTION OF WAX CRAYONS

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SINCE the first published report on "Poisoning Due to Ingestion of Wax Crayons,"¹ several other cases have been described.²⁻⁴ In addition to these, Dr. H. Russell Irwin,⁵ Children's Hospital, Los Angeles, has observed four more cases. We have also been informed that, during the past two or three years, seven cases of poisoning by wax crayons have been brought to the attention of one of the leading distributors of school supplies. Details of these latter observations are not known to us. The picture of the other cases seems to be rather uniformly that of acute, severe methemoglobinemia.

So far, four different brands of wax crayons of red-orange, orange, yellow, and violet color have been found involved. According to the manufacturers, parared is used in the red-orange and orange, and benzidine yellow in the yellow crayons. As reported before,¹ our own examination has shown the presence of parared in orange and red-orange crayons (two brands), while the red and yellow-orange crayons were free of it.

Parared was originally produced by coupling diazotized paranitraniline with β -naphthol. This compound has been found to be slightly soluble in water. Hence, the parared used in dyeing cotton is now made by coupling paranitraniline with Naphthol-AS and similar amides.⁶ The pigment used in wax crayons is chlorinated parared, as stated by the manufacturers. A sample of this pigment was examined, and also a sample of parared.* Both pigments were, as far as we could ascertain, practically insoluble in water or in standard solvents with the exception of benzol. Parared was added to stomach fluid of pH 1.1 to 8.15, shaken in a Waring Blendor, incubated for twenty-four hours at body temperature, and shaken again. After filtering, the fluid did not contain parared. The same results were obtained with chlorinated parared.

In contrast to the results recorded in the preceding Note⁷ and obtained by Irwin,⁵ we have not been able to produce methemoglobinemia in dogs or rabbits after feeding or injecting intravenously large doses of the pigments. However, in comparing these results with Dr. Spicer's and Dr. Irwin's findings, it has to be kept in mind that cats respond much more readily to methemoglobin-forming substances than dogs or rabbits.

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*Provided by E. I. DuPont de Nemours and Company, Inc.

THE TOXICITY OF WAX CRAYONS IN ANIMALS

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TOXIC manifestations in children following the ingestion of wax crayons have been reported recently.^{1, 2, 3} These symptoms were similar to those observed in acute aniline poisoning. The children were cyanotic and dyspneic, suggesting a considerable degree of methemoglobinemia. In one of the reported cases the presence of considerable methemoglobin was confirmed by chemical analysis.³ This subject, who also showed Heinz bodies, exhibited a rapid lessening of cyanosis following the administration of methylene blue. In another of the cases a moderate urinary elevation of bilirubin and urobilinogen was reported.¹ It should be noted that in none of these cases was methemoglobin formed when cats were fed the crayons which caused the illness in the children.

The problem under discussion is one of acute and not chronic poisoning. Studies on the toxicity of the crayons and the pigment used in them are reported below. Methemoglobin formation, leucopenia, and, in some cases, Heinz body formation was measured as an index of the toxicity of the material studied.

MATERIALS AND METHODS

Orange and yellow crayons have been chiefly involved in the reported cases. Studies were therefore confined mainly to these crayons. Various pigments commonly used in crayons were also tested. These pigments were lakes of the dyes parared, chlorinated parared, and benzidine yellow.

Methemoglobin was determined by a slight modification of the method of Evelyn and Malloy.⁴

EXPERIMENTAL DATA

The Toxic Effect of Crayons and Pigments on Rats.—Young rats weighing about 125 Gm. were divided into three groups and treated as follows:

Group I: Chlorinated parared and benzidine yellow pigments were each fed to a group of six rats for six days in doses of 70 mg. to each rat. The pigments were suspended with gum arabic in the drinking water of the animals.

Group II: Twelve rats were deprived of food for thirty-six hours and then placed in individual cages, each containing a single crayon. Six rats were given the orange and six the yellow crayon. The crayons were consumed in all cases within twenty-four hours.

Group III: Six rats were set aside as controls.

At the end of twenty-four hours blood samples were withdrawn from the heart of rats of all three groups and examined for both methemoglobin and Heinz bodies. No significant difference between the rats of Group I and II was observed over those of the controls.

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The Effect of Crayons on Dogs.—Two dogs were fed one crayon daily for six weeks. During the first three weeks the dogs received yellow crayons; for the last three weeks orange crayons were given. Each week a different name brand was administered. Some crayons were suspended in oil, others which did not suspend well were incorporated in chopped meat.

TABLE I. METHEMOGLOBIN IN BLOOD AFTER THE ORAL ADMINISTRATION OF CRAYONS TO DOGS*

CRAYONS	METHEMOGLOBIN (PER CENT OF TOTAL HEMOGLOBIN)	
	DOG 1	DOG 2
Control	2.1	1.3
Yellow crayon 1	1.9	1.3
Yellow crayon 2	1.5	0.9
Yellow crayon 3	2.9	1.9
Orange crayon 1	1.8	1.3
Orange crayon 2	2.4	1.0
Orange crayon 3	1.6	0.9

*The dogs were fed a single crayon daily. At the end of each week a different brand or color of crayon was substituted. Methemoglobin determinations were made weekly.

Blood methemoglobins which were measured weekly showed no significant rise over the control levels (Table I). Hemoglobin, red cell count, and white cell count (total and differential) also showed no significant change. Para-aminophenol has been reported in the urine of the children who ingested crayons.¹ Examination of the urine of the dogs by methods previously described⁵ revealed neither para-aminophenol (free and conjugated) nor aromatic amines.

The Effect of Pigments Administered Intravenously to Dogs.—Two dogs were given intravenously 75 mg. of pigment suspended in propylene glycol. One dog received parared pigment and the other chlorinated parared. Examination of blood periodically over a twenty-four-hour period showed no methemoglobin formation and no change in the white cells or hemoglobin. The lack of toxicity after parenteral administration suggests that the toxicity of the wax crayons does not depend upon absorption of this pigment from the gastrointestinal tract.

The Effect of Crayons on Cats.—Since cats are particularly susceptible to methemoglobin-forming agents, the effect of crayons was also studied on these animals.

TABLE II. METHEMOGLOBIN IN BLOOD AFTER THE ORAL ADMINISTRATION OF CRAYONS TO CATS*

EXPT. NO.	METHEMOGLOBIN (PER CENT OF TOTAL HEMOGLOBIN)		
	CONTROL	AFTER YELLOW-ORANGE CRAYON	AFTER YELLOW CRAYON
1	2.6	2.5	1.0
2	2.0	5.6	1.1
3	1.7	2.4	1.5
4	2.1	3.5	1.0

* of a yellow-orange crayon mixed in salmon daily for four weeks. A yellow crayon daily for three days. Methemoglobin determinations were made at end of the period of each crayon feeding.

Four cats were given one-half of a yellow-orange crayon incorporated in fish daily for four weeks. Blood was then withdrawn under Nembutal anesthesia, and the methemoglobin determined. No significant changes were observed, either in the methemoglobin (Table II), in the hemoglobin, or in the white cells, as compared with control blood samples drawn prior to the experimental period.

The above cats were then given, in a similar manner, one-half of a yellow crayon daily for three days. Again no significant change in the blood picture was observed (Table II).

DISCUSSION

The toxic symptoms found in children can be ascribed to the formation of methemoglobin. This suggests the possibility that the azo dyes used in the crayon pigments change in the body to the toxic, aromatic amines. However, the feeding of wax crayons or pigments to animals failed to produce experimental methemoglobinemia. Although children commonly ingest wax crayons, the occurrence of toxic symptoms is rather rare. This suggests that the occasional toxicity of the crayons may be classed as an idiosyncrasy.

SUMMARY

The feeding of orange, yellow, and yellow-orange crayons to rats, dogs, and cats failed to produce methemoglobinemia. Administration of crayon pigments orally to rats and intravenously to dogs similarly failed to produce methemoglobinemia.

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NONSENSITIZATION TO REPEATED TUBERCULIN TESTING

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ALTHOUGH, it has been shown that tuberculin testing may cause local or systemic flare-ups¹⁻³ in patients with proved tuberculosis, the question often arises as to whether the various tuberculin tests can induce hypersensitivity to themselves in nontuberculous individuals.

Some investigators⁴⁻⁷ have felt that it was possible to induce tuberculin hypersensitivity to tuberculin while others^{8, 9} demonstrated that it was unlikely.

Since this is an important factor in patients being observed for the possible presence of tuberculosis, another study in an attempt to clarify this point would not be amiss. Furthermore, since the tuberculin patch test had not been used in any of the previous studies, this would be an opportune time to determine its status with regard to sensitivity.

Therefore, two groups of infants who were being kept as boarders on the wards and who had not been exposed to tuberculosis were included.

The Mantoux (intradermal) test using O.T. (prepared by the Bureau of Laboratories of New York City Department of Health) was used on a group of ten infants whose ages ranged from 2 to 9 months, and on one child 3 years of age.

In each case a 1:10,000 dilution was first given, and when found to be negative was followed by a 1:1,000, and then a 1:100 dilution. When the child's test proved negative to the latter, it was repeated at forty-eight hour intervals. The length of time between the first and last test varied from one to six months and the number of tests done from eleven to sixty, as noted in Table I.

TABLE I. MANTOUX TESTING

Case	1	2	3	4	5	6	7	8	9	10	11
Sex	F	M	F	F	M	M	F	F	M	F	M
Color	W	W	W	W	W	W	W	C	C	C	C
Age at onset (in months)	5	5	2	3	6	7	7½	36	9	1	2
Number of tests done											
December	3	3	3	3	3	3	3	3	3		1
January	8	8	8	8	8	8	8	7	8	1	1
February	3		3	3	3		1		3	2	2
March	15		15	15	7			15	12		15
April	12		12	12(3*)				12			12
May	15		15	2				5			15(1*)
June	4		4								4
Total number	60	11	60	43(3*)	21	11	12	42	26	3	49(1*)
Time between first and last test (in months)	6	1	6	5¼	2½	1	1½	4½	3	½	6

*Indicates the number of questionable reactions which are included in the total figure.

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In Case 4, there were three occasions on which an area of erythema was noted which disappeared after forty-eight hours and then was subsequently followed by negative results.

In Case 11, this occurred once and was similarly followed by negative results, giving the impression that it was a mild, local, inflammatory reaction.

Tuberculin patch test (Vollmer) was used on another group of eleven infants ranging in age from 2 to 10 months and on one child of 3 years.

It was applied over the interscapular area, read forty-eight hours after removal, and when negative was immediately followed by another one applied to another area.

This procedure was followed except for several patients of both groups, who were isolated in a contagious disease hospital during periods of contagion, at which time tests were not done.

From eight to twenty-nine patch tests were done on the infants over a period ranging from one to six months, as illustrated in Table II.

TABLE II. TUBERCULIN PATCH TESTING

Case	1	2	3	4	5	6	7	8	9	10	11	12
Sex	M	M	M	M	M	M	F	F	M	F	M	F
Color	W	C	W	W	C	W	C	W	C	C	C	W
Age at onset (in months)	2	7	4	4	5	10	7	3	8	36	2	4
Number of tests done												
December		2	2	2	2	2	2	2	2	2	2	2
January	1	7	7	7	7	7	7	7	6	6	7(1*)	6
February	3	3	3	2	3	2	1	2			3(1*)	
March	7		5		2	6	6(1*)	3		7(2*)	1(1*)	
April	7		7		3	3	3	7		5(1*)	4(1*)	
May	7		3			7	3	4		7	7	
June	2					2				2	2	
Total number	27	12	27	11	17	29	22(1*)	25	8	29(3*)	26(4*)	8
Time between first and last test (in months)	5	1½	4½	1½	4	6	4½	4½	1	6	6	1

*Indicates the number of questionable reactions which are included in the total figure.

In Case 7, there was one questionable reaction (area of erythema which disappeared within forty-eight hours) on March 29 but all subsequent tests were negative.

In Case 10, questionable reactions occurred on March 25 and 29 and on April 11, but all others that followed were negative.

In Case 11, similar questionable reactions occurred on January 27, February 2, March 5, and April 15, but all other tests were negative. Because of these questionable reactions, Case 11 (same as Case 11 in Table I) was also tested with O. T. forty-nine times and except for May 1, when a slight, transient erythema was noted, all tests were negative.

SUMMARY AND CONCLUSION

1. Twenty-three nontuberculous infants were tested for hypersensitivity to repeated tests of tuberculin using the patch test and the O.T.

2. No evidence of any definite or lasting sensitivity could be detected.

3. Therefore, it is felt that it should be safe to follow any suspicious cases with routine skin testing as long as no evidence of tuberculosis is proved.

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FAILURE OF GAMMA GLOBULIN TO PREVENT VARICELLA

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MOST physicians regard chicken pox as a rather benign disease which, except for the infrequent complication, is without serious consequence. However, in the institution, the pediatrics ward, the isolation hospital, or orphanage, it may assume an importance greater than that of a mere inconvenient nuisance. Cross-infections and sporadic outbreaks, once begun, may become recurrent every few weeks. This results in the tying up of wards for considerable periods of time. It may even cause the closing of an entire service. In any event, it seriously handicaps the normal operation of the unit.

For this reason, as well as for the protection of the occasional child at a period when varicella infection may not be desirable, an effective prophylactic measure would be of considerable value. The preparation of a vaccine is not likely, at least not until varicella virus has been transmitted to lower animals or their embryos, which transmission has not as yet been accomplished. From time to time claims have been made concerning the efficiency of pooled human adult serum or convalescent serum.¹ On the other hand, equally poor results have been reported,² and since these have been based on more thoroughly executed and carefully controlled experiments, they have been more convincing.

The excellent passive immunity afforded by human serum gamma globulin against measles³ and infectious hepatitis,⁴ its high scarlatina and diphtheria antitoxic titers, and its availability in generous amounts through the agency of the American Red Cross, prompted us to determine whether gamma globulin may not also contain an antivariella factor and thus be of value in the prevention or modification of chicken pox. In two previous attempts, no significant results were obtained by Greenberg⁵ with gamma globulin against rubella and varicella, while excellent results are claimed by Funkhouser.⁶

An opportunity to conduct our first trial appeared in April, 1946, when, in an orphanage housing forty-one children of both sexes, aged 3 to 5 years, five cases of varicella occurred, the first on April 7, a second on April 9, and three on April 10. The source of exposure was unknown.

On April 11, four days after exposure, the remaining children were divided into two groups. Group A consisted of thirteen children with histories of previous varicella infection. Group B was comprised of twenty-three children without histories of chicken pox, and this group was further subdivided into Group I, having ten children to be treated with gamma globulin, and Group II, with thirteen children to serve as untreated controls. After the treated group received 5 c.c. of gamma globulin intramuscularly, all of the children were permitted free and intimate contact with those having varicella.

From the Jack & Helntz Laboratory, Department of Contagious Diseases, City Hospital and the Department of Pediatrics, Western Reserve University.

Four secondary cases appeared in the control group, one each on April 27, 29, 30, and May 11. A fifth case occurred on May 27, and a sixth on June 8. It was subsequently learned that three of the ten children inoculated had had chicken pox previously, leaving 7 in this group, none of whom contracted chicken pox.

Despite these promising results, it was felt that no conclusions were warranted at this point until they were amply confirmed by further trials. Later, two other occasions presented themselves and attempts to verify the original findings were made. These resulted in complete failure.

The second trial was conducted in a day nursery in May, 1947. There were approximately seventy-five children of both sexes, mostly of preschool and some of school age in attendance. A 6-year-old girl who had been previously well had complained of a stomach-ache on April 29. She had no fever at this time. On April 30, she appeared normal and had no complaints. That evening she broke out with "a few spots" on her body. She was brought into the nursery on May 1. On examination, she was found to have a generalized eruption and was sent home immediately, having had no contact with any of the other children at the nursery at that time. A physician who saw her at home the next day made a diagnosis of chicken pox. On May 6, the fifth day after exposure, upon being informed of the situation, twenty-three of the children at the nursery who had histories of not having had varicella previously were divided in half. Eleven of these received 5 c.c. of gamma globulin intramuscularly and twelve were untreated. Between May 14 and 27, six cases of varicella appeared in the treated group and six cases were observed between May 10 and 20 in the control group.

The third trial was carried out in the orphanage mentioned above in March, 1948. By this time, there had been a considerable turnover of inmates so that the majority of them had been newly admitted since the outbreak in 1946. On the sixth day of that month a child came down with chicken pox. On March 8, the second day after exposure, when our attention was called to this, there were forty children, fourteen of whom were said to have had chicken pox; the remaining twenty-six were divided into two groups of thirteen each. In the first group, each child received 10 c.c. of gamma globulin intramuscularly. The second group served as control. Between the nineteenth and twenty-third day of March, chicken pox occurred in seven of the inoculated and in eight of the uninoculated group.

It is interesting to note that four of the fourteen who supposedly had had chicken pox previously became infected on March 20. This demonstrates that because of the unreliability of histories in institutions, it is important to utilize large numbers of adequately controlled groups to ensure the validity of results.

Recently, at about the time of completion of our third series, a report by Funkhouser² appeared, describing four separate episodes where the treatment of groups of seven, sixteen, twenty-three, and thirty-one exposed children with 2 to 5 c.c. of gamma globulin gave 85 to 100 per cent protection against varicella. He was fortunate in being able to inject these children on the first day following appearance of the varicella lesions on the primary case. Perhaps this early

treatment may account for the disparity in our results, since our contacts were not inoculated until two to five days after the eruption appeared on the first case. Unfortunately, Funkhouser failed to include uninoculated controls. Because varicella is admittedly one of the most contagious diseases, with a high morbidity among susceptible contacts, Funkhouser's results appear highly suggestive. Nevertheless, the lack of controls detracts from the significance of his findings, for accurate interpretation and the evaluation of the validity of such results is rendered difficult, if not impossible, by the omission of suitable controls.

While we do not consider our results final, it would appear at this time that gamma globulin, given to children in 5 e.e. or 10 e.e. doses intramuscularly, is not an effective prophylactic measure against varicella, since it failed to prevent or modify the disease in two out of three controlled experiments where it was given two to five days after exposure. We do not know how to explain the contradictory results in our first trial where there was apparent protection by gamma globulin. Because histories in orphanages are frequently unreliable, it is conceivable that many more of the children than the three later discovered in the treated group may have had varicella previously.

It is possible that earlier administration may be of benefit, but even if true, it would not always be feasible and would be of limited practical value. This point, however, deserves further elucidation and opportunities will be sought to investigate the effect of gamma globulin administered on the first day following exposure to the erupted case and possibly also prior to exposure.

SUMMARY

In three series of experiments, children exposed to varicella were given 5 e.e. or 10 e.e. of gamma globulin intramuscularly, two to five days after the primary case with the erupted lesion appeared.

In the first series, five secondary cases appeared in thirteen untreated controls, while seven children inoculated with 5 e.e. of gamma globulin four days after exposure remained free of infection.

In the second series, six of eleven children treated five days after exposure and six of twelve controls developed chicken pox.

In the third series, seven of thirteen children treated two days after exposure and eight of thirteen controls developed chicken pox.

No explanation is evident for the apparent success in the first series, but it is possible that the histories of not having had varicella previously may have been unreliable.

Gamma globulin does not appear to afford passive immunity under the conditions of these experiments.

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ELECTROENCEPHALOGRAPHY IN BEHAVIOR PROBLEM CHILDREN

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SINCE 1937, when Solomon, Jasper, and Bradley¹ reported a high incidence of electroencephalographic abnormality in children with behavior disorders, there have been repeated reports in the literature confirming this original finding.²⁻¹⁰ All reports but one indicate a 50 to 70 per cent incidence of electroencephalographic abnormality in behavior problem children. Jenkins and Paedella,⁷ by contrast, report 22 per cent EEG abnormality in a group of fifty delinquent boys. The type of abnormality has been described as paroxysmal^{2, 8, 9} or slow,^{2-4, 6, 8, 9} with rare reports of focal abnormalities.^{2, 3} The explanation of the high incidence of electroencephalographic abnormality has varied widely. Some authors suggest that certain children with behavior disorders possess the personality and electroencephalographic abnormalities of epileptics without clinical seizures.^{2, 3} It has been suggested that the electroencephalographic abnormality indicates immaturity,⁶ lack of control,¹¹ and disturbance of cortical function,⁴ and that these traits characterize the personality disturbance as well as the electroencephalogram. Others suggest that the EEG and personality abnormalities are inherited traits in many instances.^{8, 10} Finally, the opinion that EEG abnormalities in behavior problem children may be due to organic brain pathology is based on the following facts. Organic pathology is known to be capable of producing EEG abnormality; some investigators have reported a correlation between EEG abnormality and a history suggestive of brain damage;^{2, 5, 9} and an association has been reported between certain personality features, thought to be due to organic impairment, and EEG abnormality.⁷ There is no direct evidence on the basis of other findings that organic impairment does, in fact, exist in some of these cases.

Greenblatt, Levin, and Atwell¹² have reported a series of adult patients suspected of having brain damage who were studied by means of psychological tests and EEG. They report greater accuracy for the psychological tests than for the electroencephalogram, but the greatest diagnostic accuracy was achieved by the use of both tests. Of the patients in whom both tests were abnormal, 91 per cent were diagnosed as having brain damage. Forty-three per cent of the patients in whom both tests were normal were diagnosed as having brain damage. The authors point out, however, that many of the patients had brain disorders which were either arrested or slowly progressive, and that a normal EEG may be found in spite of the presence of demonstrable organic pathology under these conditions.

¹The work herein reported was done in part to fulfill the requirement for the degree of M.D., 1948, Yale University School of Medicine.

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Sarason and Sarason,¹³ working with familial defectives, were able to demonstrate a correlation between "organic" findings on psychological testing and EEG abnormality. The authors report a 60 per cent incidence of EEG abnormality in patients whose psychological test results suggested organic impairment, as against 18 per cent abnormality in patients who had no "organic" signs on psychological testing. The same authors¹⁴ found the same correlation between EEG abnormality and organic signs on psychological testing in a group of cerebral palsied children, all of whom had neurological evidence of brain pathology. The authors conclude that both the psychological examination and the EEG are likely to demonstrate superficial organic brain pathology.

It was considered likely that the psychological test might provide valuable evidence as to the presence or absence of brain pathology in behavior problem children with abnormal electroencephalograms.

MATERIAL AND METHODS

The 160 subjects utilized in this study were all patients who had been referred for diagnostic electroencephalography by Dr. William B. Curtis.* Through his kindness, the clinical histories of these cases were made available and were reviewed for the following items: (1) family history of psychosis, alcoholism, epilepsy, or psychopathic personality; (2) medical history of chorea, encephalitis, meningitis, head injury with unconsciousness, severe illness with delirium or high fever occurring before the age of 2 years, or a history of abnormal birth (For the purposes of this study, an abnormal birth was indicated by a history of prematurity, multiple birth, instrument or breech delivery, cesarean section, or a history of neonatal anoxia. A history of one or more convulsions excluded the patient from the series); (3) abnormal neurological signs.

All the patients in this group had had psychological examinations as part of their diagnostic work-up. The original tests were reviewed by Dr. Seymour Sarason. Unfortunately, most of the children had been given the Stanford-Binet test, Form M. Because of the lack of performance items on this test, Dr. Sarason was able to separate only those in whom the evidence for organic factors was so strong that it could be clearly seen, even in the predominately verbal material.

Electroencephalograms were obtained with a six-channel Grass Electroencephalograph. Electrodes were placed on frontal, central, parieto-occipital, and temporal areas on both sides. Grounded, interconnected ear leads were used. All the electroencephalograms were reviewed and classified according to the Gibbs' classification,¹⁵ as moderately slow (S_1), moderately fast (F_1), very slow (S_2), very fast (F_2), paroxysmal (petit mal, petit mal variant, psychomotor, spikes, or grand mal), or focal. Records in which slowing was confined to the occipital leads were classified separately. The normal control series consisted of 373 unscreened normal children, aged 2 weeks through 15 years. Of these records, 120 were obtained at the Boston Children's Hospital and were

*Dr. Curtis is in charge of Psychiatric Service in the Community, a Community Chest agency to which children in need of psychiatric opinion or aid may be referred by schools, courts, parents, other agencies.

made available through the kindness of Dr. Frederick A. Gibbs, and Mrs. Erna L. Gibbs. Two hundred fifty-three records were obtained at the Pediatrics Clinic of the New Haven Hospital, with the collaboration of Dr. Donald L. Dunphy.

TABLE I

SEX	NO. PATIENTS	ELECTROENCEPHALOGRAM			
		NORMAL		ABNORMAL	
		NO.	%	NO.	%
Male	123	85	69	38	31
Female	37	19	51	18	49

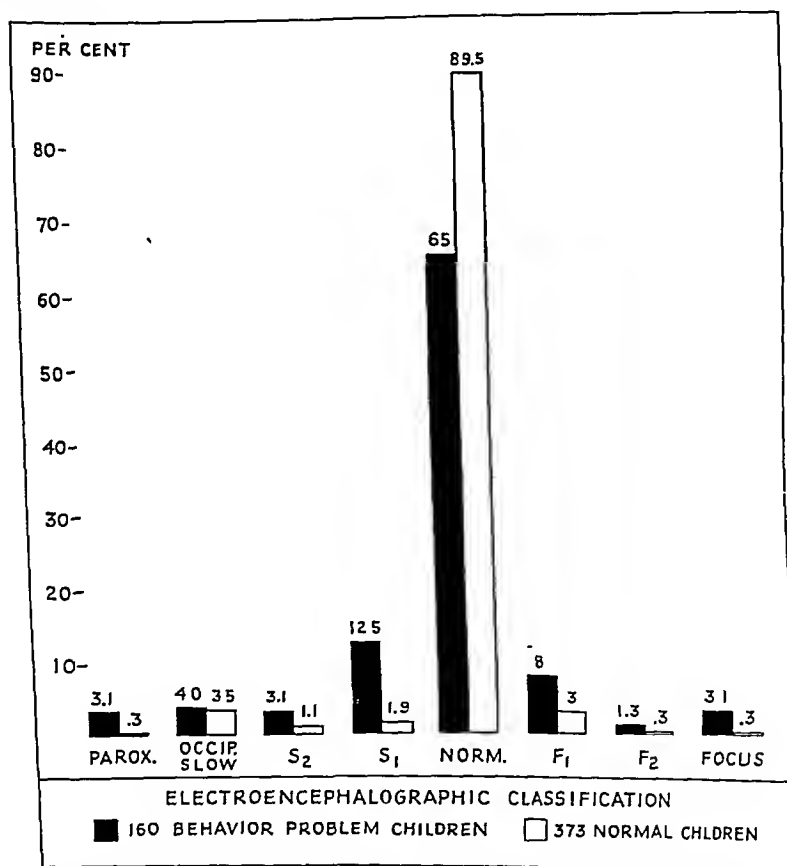
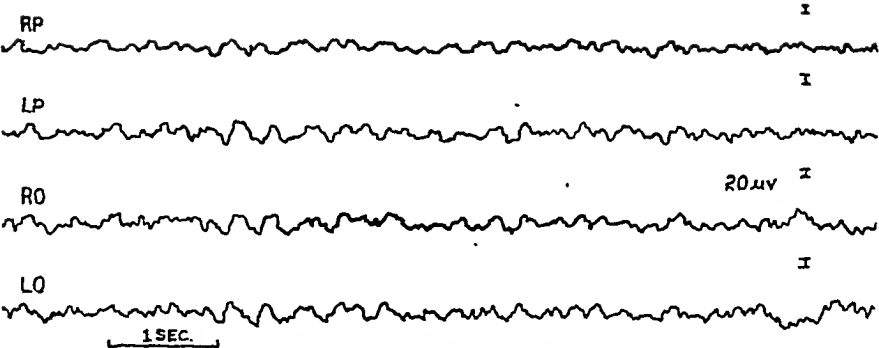


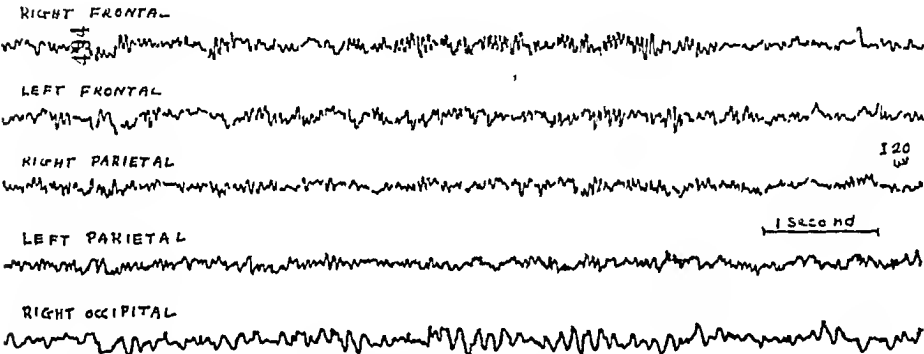
Fig. 1.—*Parox.*, paroxysmal (petit mal, spikes, paroxysmal slow); *Occip. slow*, occipital slowing; *S₂*, very slow; *S₁*, moderately slow, *F₁*, moderately fast; *F₂*, very fast.

RESULTS

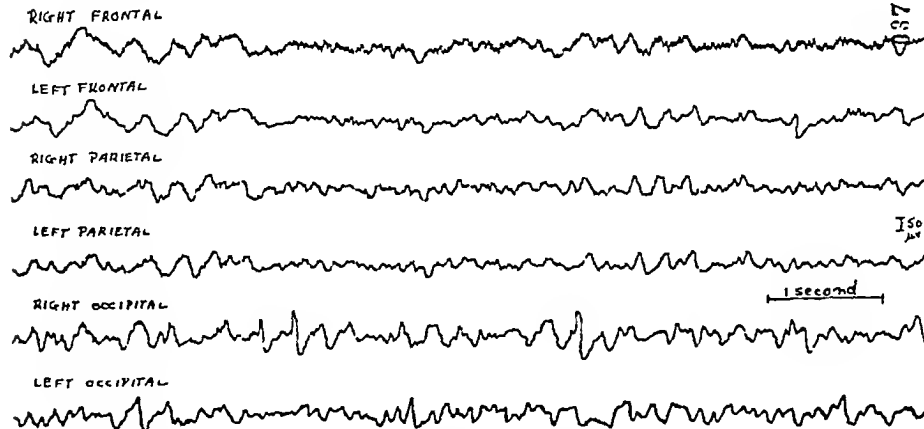
Incidence of EEG Abnormality.—Of the 160 patients in this series, 56, or 35 per cent, have abnormal EEG's. The distribution of EEG abnormalities is shown in Fig. 1, where the distribution of EEG abnormality in normal children is given for comparison. Examples of abnormal electroencephalograms from the behavior problem group are illustrated in Fig. 2.



♂ AGE 15 ABNORMALLY SLOW



♂ AGE 8 ABNORMALLY FAST



♂ AGE 9 FOCAL ABNORMALITY

Fig. 2.—Samples of EEG abnormality in behavior problem children.

Sex Distribution.—Male patients outnumber female patients by three to one in this series. The girls have a higher percentage of EEG abnormality than the boys (Table I), but there is no marked difference in type of EEG abnormality between boys and girls.

Family History.—A positive family history (immediate relative with alcoholism, psychosis, psychopathic personality, or epilepsy) was recorded in forty-six instances. EEG abnormality is not correlated with these items in the family history in this series (Table II).

Positive Medical History.—A positive medical history (abnormal birth, head injury, illness with delirium, or high fever before the age of 2 years) was recorded in thirty-four instances. There is a slight correlation between a positive medical history, as defined, and an abnormal EEG (Table II). No item in the personal history showed a higher degree of correlation with an abnormal EEG than any other.

Neurological Examination.—Seventeen patients had positive neurological findings. These consisted of coarse choreiform movements of the extremities in fourteen, abnormal associated movements in five, hyper-reflexia in two, and nystagmus in one. These abnormalities tend to be associated with abnormality in the EEG (Table II).

Psychological Test Results.—Stanford-Binet scores in the series ranged between 58 and 140. The score was below 80 in ten and above 120 in six patients. A total of ninety-three patients had psychological examinations which were adequate to permit evaluation of possible organic factors. Thirty-two of these, or 34 per cent, had abnormal EEG's. Thirteen of the ninety-three children had psychological test results which were considered indicative of organic impairment. There is a correlation between psychological evidence of organic impairment and electroencephalographic abnormality (Table II).

TABLE II

	NO.	ELECTROENCEPHALOGRAM			
		NORMAL		ABNORMAL	
		NO.	%	NO.	%
Behavior problem children	160	144	65	56	35
Family history	160				
Positive	46	30	65	16	35
Negative	114	74	65	40	35
Personal history	160				
Positive	34	19	56	15	44
Negative	126	85	67	41	33
Neurological examination	160				
Positive	17	7	41	10	59
Negative	143	97	68	46	32
Psychological examination	93				
Organic signs	13	6	46	7	54
No organic signs	80	56	70	24	30

DISCUSSION

The present investigation confirms reports in the literature of a higher incidence of EEG abnormality in behavior problem children (35 per cent) than in normal children (10.5 per cent). The percentage of abnormality is not as high as that reported by the majority of authors, who have found 50 to 70 per

cent abnormality.²⁻¹⁰ This is especially unexpected since the behavior problem children who comprise this series are not the average of behavior problems, but are children in whom the referring physician suspected "central nervous system dysrhythmia" as a factor and asked for an EEG as an aid in diagnosis.

Male patients outnumber female by three to one in this series, yet 49 per cent of the girls have an abnormal EEG as against 31 per cent of the boys. Only slight sex differences have been observed in normal children¹⁶—differences hardly great enough to account for the discrepancy in our series. It is probable that it takes a more severe personality disturbance to require referral of a preadolescent girl for psychiatric help than is the case with boys. This may explain the small number of girls, but it does not explain why the girls have a higher percentage of EEG abnormality unless the severity of behavior disturbance is correlated with EEG abnormality. There is no evidence in the present series which would indicate that this is so.

EEG abnormality was observed in fifty-six of the 160 children who comprise this series. The type of EEG abnormality observed in the present series was nonspecific in type and moderate in degree in thirty-three, or more than one-half of the cases. These abnormalities (moderately fast and slow) cannot be considered even suggestive of the type of pathology. Seven patients had very slow or very fast activity, which was no more specific than the moderate abnormalities but much more indicative of some type of pathology. Nine patients had slowing confined to one brain area, or spikes—abnormalities which are fairly definitely indicative of organic brain pathology in the absence of a history of seizures. Only one patient had the three-per-second spike and wave abnormality which is almost always diagnostic of epilepsy.

As to the interpretation of the EEG abnormalities, the findings in this study do not support the view that behavioral difficulties in children are related to epilepsy in the absence of overt seizures as suggested by Jasper, Solomon, and Bradley,² and Strauss, Rahm, and Barrera.³ Gottlieb, Ashby, and Knott,⁹ and Kennard¹⁰ also lay stress on hereditary or "genogenic" causes for EEG (and presumably behavioral) abnormalities in these cases. The present study does not confirm the finding of a correlation between EEG abnormality and a positive family history⁹ of alcoholism, psychosis, or psychopathic personality. Indeed, since these conditions are not in themselves associated with EEG abnormality in our experience, no such correlation was expected. There were too few positive family histories of epilepsy in this series to allow evaluation of this item in the family history. Patients with a personal history of convulsions were excluded from this series. The only positive correlations found in this study were between EEG abnormality and a past personal history of possible brain damage, abnormalities on neurological examination, and "organic" signs on psychological examination. It seems plain, then, that many children with behavior problems and EEG abnormality have organic brain pathology. This supports the opinion of Brill and collaborators,⁵ Jenkins and Pacella,⁷ and Gottlieb, Ashby, and Knott.⁹ It leaves unexplained the patients with abnormal EEG's who have no evidence on the basis of history, physical examination, or psychological test of organic abnormality.

Except for patients with organically determined hyperactivity, impulsiveness, and distractibility, there is no reason to suspect a specific relation between the brain pathology and behavioral difficulty. "In the present state of our knowledge it is probably wise to assume that in interpreting behavior disorders an abnormal electroencephalogram is an indication of a . . . central nervous system which proves a handicap in social adjustment just as would poor vision, faulty muscular coordination, or a similar constitutional defect."¹⁷

Nor is there any reason to believe that an abnormal EEG implies a poor prognosis. The EEG may be of aid in that it may indicate the possibility of an organic handicap to which the patient can be helped to make an adequate adjustment. "A defeatist attitude is in no sense justified merely because of evidence of electrocortical dysfunction. . . It is possible that EEG may become a valuable aid in determining or recognizing many of these handicapped personalities."¹⁷

The diagnosis of organic handicap cannot be made on the basis of the EEG alone, since the history and neurological examination may suggest this factor when the EEG is normal. The present study suggests that psychological testing may be a valuable addition to the diagnostic armamentarium. Unfortunately, the psychological test material available for this study was not detailed or complete enough to allow a definitive evaluation. The results are suggestive enough to warrant further investigation, and this is being carried out at present.

SUMMARY AND CONCLUSIONS

1. One hundred sixty children with behavior problems were studied electroencephalographically in the course of the diagnostic work-up. Fifty-six of these, or 35 per cent, had an abnormal EEG as contrasted with 10½ per cent in a normal group.

2. The EEG's were moderately slow or fast in thirty-three, very slow or fast in seven and slow in the occipital leads only in six. Nine patients had focal slowing or spikes, considered indicative of organic brain pathology in the absence of a history of seizures. One patient had petit mal waves.

3. Electroencephalographic abnormality does not correlate with a positive family history in this series. It does correlate with positive findings on neurological examination, a personal history of possible acquired brain pathology, and "organic" signs on psychological testing.

4. It is concluded that EEG abnormality in behavior problem children may indicate organic brain pathology. It is suggested that this organic involvement usually bears no more specific relation to the behavior disturbance than any other type of handicap.

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Case Reports

CANDIDA ALBICANS AND CRYPTOCOCCUS NEOFORMANS OCCURRING AS INFECTIVE AGENTS IN AN EIGHT-YEAR-OLD BOY

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INTRODUCTION

IT IS the purpose of this presentation to record the occurrence of *Candida albicans* and *Cryptococcus neoformans* in the same individual. Either of the fungous infections individually could have been responsible for the symptoms observed. Cutaneous infection¹ by *Candida albicans* is common. This fungus causes other clinical manifestations which may be either localized or disseminated, acute or chronic, inflammatory or indolent, and which may affect the mucous membranes,² the gastrointestinal tract, the respiratory tract,^{3, 4} or the central nervous system,⁵⁻⁷ singly or in combination.^{8, 9}

Cryptococcus neoformans also is pathogenic for man, involving more frequently the central nervous system and the lungs,¹⁰⁻¹⁴ and less frequently the viscera,¹⁵ nasopharyngeal structures, lymph nodes, muscles, bones, and skin.¹⁶⁻¹⁸

In this case the first infection observed was *Candida albicans* as proved by laboratory studies. The terminal infection with central nervous system manifestations was *Cryptococcus neoformans*.

REPORT OF CASE

B. D. R., an 8-year-old white boy, was admitted to the hospital on Jan. 23, 1945. He was emaciated and chronically ill in appearance. The chief complaint was that of diffuse, crusted, skin lesions over his face, scalp, left shoulder, fingers, and toes. The onset occurred four years prior to admission with the development of a "ringworm" type of lesion on his chin which subsequently spread over his entire head, shoulders, upper chest, and arms. These lesions cleared after x-ray and iodide therapy, only to be followed in a few weeks by a generalized eruption, from which *Candida albicans* was cultured. Later a large, dark, crusted, hornlike lesion developed over one fingernail. Gradually all but one fingernail and all of the toenails were involved by a similar process (Figs. 1 and 2). The nail and cutaneous lesions persisted as observed on admission.

The past history revealed that the patient had pneumonia at 8 months and again at 21 months of age. During the fourteen months prior to admission he had four attacks of "pneumonia," which were acute pulmonary episodes with high fever (106° F.), cough, purulent sputum production, and chest pain, lasting several days. The patient had a low-grade fever throughout his illness as well as an intermittent, slightly productive cough. Two months before admission a roentgenogram of the chest showed a large infiltrative type of lesion suggesting abscess formation in the central portion of the right lung.

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During the three years before admission six abscesses developed involving the face, left knee, and anal region. All of these drained spontaneously except the peri-anal abscess, which required incision. At the time of abscess formation the mucous membranes of the mouth and tongue became involved.

The patient lived in Kansas during the first year of his illness and then moved, with his family, to Los Angeles.



Fig 1.—Photograph of the patient showing the skin lesions of the face, neck, and fingernails.



Fig. 2.—Photograph of the lesions of the toenails and the toes.

Admission examination.—The patient was a poorly developed, poorly nourished, chronically ill white boy of 8 years. Over the face and forehead were numerous diffuse, nonerythematous papular lesions which were covered by a rather adherent serum crust. Some of the lesions were excoriated. The same process involved the scalp, where it was associated with alopecia. These lesions averaged approximately 0.5 cm. in diameter. Over the shoulders and the left arm were larger circinate lesions from 2 to 3 cm. in diameter, with pale centers and erythematous borders. The toenails and all of the finger-

nails except that of the left index finger appeared as brownish-black horns 1 to 1.5 cm. thick. There was marked clubbing of the distal phalanges. The oral mucosa, tongue, and gums were profusely covered with a white, furry mucoid covering and were hyperemic. The axillary and inguinal lymph nodes were small, shotty, and nontender. The chest was very thin with retracted interspaces. Slight dullness to percussion was noted over the entire right lung. Auscultation revealed diminished breath sounds and coarse râles both anteriorly and posteriorly over the right lung. The heart was slightly enlarged to percussion; the rate was 140 beats per minute and the rhythm was regular. The spleen was palpable 1.5 cm. below the left costal margin; the liver and kidneys were not palpable. The musculature throughout showed marked atrophy. There were no abnormal neurologic findings.



Fig. 3.—Photograph of a roentgenogram of the patient's chest taken on March 28, 1945. Bilateral soft nodular densities are seen extending outward from both hilar regions. The densities are much more pronounced on the right, involving nearly the entire lung.

Laboratory tests, including Wasserman test, were within normal limits with the exception of the erythrocyte sedimentation rate, which was 46 mm. in one hour (Westergren). There was also a slight trace of albumin in the urine. Skin tests with oidiomycin, trichophyton, coccidioidin, and tuberculin were negative. On admission blood cultures failed to show growth on blood agar, beef broth, brain broth, and on Sabouraud's medium.

Roentgenographic reports of the chest revealed soft nodular densities extending outward from both hilar regions, more pronounced on the right (Fig. 3). Roentgenograms of the long bones were negative.

Course.—The patient remained afebrile during the first week in the hospital. During the second week he began to run a septic temperature curve

daily with elevations of 104° F. Râles were heard throughout the chest and were more marked on the right. A roentgenogram taken Feb. 2, 1945, revealed the densities of the right lung to have increased. The white cell blood count rose to 16,400 per cubic millimeter with 77 per cent polymorphonuclear neutrophils, 18 per cent lymphocytes, and 5 per cent monocytes. Blood cultures were negative. Sulfadiazine therapy was inaugurated and the patient's condition improved. The laboratory reported that cultures from the skin lesions, mouth, and sputum were positive for *Candida albicans*. The identity of the infecting organism was confirmed by sugar media reactions and by inoculation into rabbits. Following this acute pulmonary episode the patient's general condition remained stationary with a persistent low-grade fever of 101° F. Gradually there was a recurrence of leucocytosis, which ranged between 15,000 and 16,000 white blood cells per cubic millimeter with 70 to 80 per cent neutrophils.

Forty-four days after admission an intradermal skin test was performed, using 0.1 c.c. of a 1 to 10 dilution of a heat-killed, saline suspended, autogenous, *Candida* antigen. No reaction occurred after forty-eight hours; a repeated dose of 0.1 c.c. of the undiluted antigen produced a zone of erythema and induration 0.5 cm. in diameter after forty-eight hours. An attempt was made to desensitize the patient to his autogenous antigen prior to specific therapy with iodides. The procedure followed a modification of the desensitization procedure outlined by Smith, Baker, and others.¹⁰ Following the third injection of the autogenous antigen the patient had an acute exacerbation of the pulmonary symptoms. Peneillin as well as sulfadiazine was administered to combat secondary infection. The autogenous vaccine was continued until after the fifth injection, when it became apparent that the patient was in quite a critical condition. He was given two blood transfusions of 150 c.c. each. The attack gradually subsided, although the pulmonary findings remained stationary. The patient's course, following the second pneumonic episode, was gradually but continuously downhill, with weight loss, anorexia, intermittent vomiting, malaise, increasingly productive cough, and continued low-grade fever. In March, 1945, another attempt to desensitize him was begun but failed to alter the downhill course. Intravenous gentian violet and oral potassium iodide were instituted in April, 1945, after a urine culture was reported positive for *Candida albicans*.

On April 30 the patient complained of severe headache and one day later became lethargic. The spinal fluid was cloudy and under increased pressure. Cultures yielded *Candida albicans* and a roentgenogram of the chest revealed a miliary spread throughout with no apparent involvement of the pleura. Cultures of the spinal fluid and urine taken on May 3 yielded both *Candida albicans* and *Cryptococcus neoformans*. On May 5 the temperature rose to 104° F. and the patient, who had been comatose for thirty-six hours, expired.

NECROPSY

The body was that of a poorly developed, markedly emaciated white male child. The skin and nail lesions had the same appearance as on admission. The right lung, which was bound to the parietal pleura by large blanket adhesions, weighed 360 grams; the normal weight for the age group is 147 grams. The left lung weighed 360 grams; the normal weight for the age group is 152 grams. On palpation the lungs were firm and contained very little air. The lung sectioned with great resistance and the cut surface revealed large, firm, yellow and white areas from 1 to 4 mm. in diameter (Fig. 4). The tracheobronchial lymph nodes were large, measuring from 1 to 1.5 cm. in

diameter. The pulmonary mucosa was injected and roughened. Small white nodules were scattered throughout the liver. The spleen was almost twice the normal weight and contained many small white nodules throughout its pulp. The mesenteric lymph nodes were enlarged. There were also small white nodules throughout the renal tissue. The brain revealed small, firm, yellowish-white nodules averaging 1 mm. in diameter scattered profusely over the posterior parietal region and over the occipital lobes and cerebellum; occasional areas of firm white exudate were scattered over the meninges. On section the process was seen to involve only the surface of the brain. All sections of the nodules described grossly revealed the same type of lesion microscopically. These structures were composed of loose swirls of connective tissue containing transparent yeastlike cells with capsules, occasional giant cells, and epithelioidlike cells, and surrounding these cells a collar of dense fibrous tissue strands enmeshing many small round cells (Fig. 4). In some of the larger lesions, large areas of necrosis were seen. The sections of the brain showed marked vascular congestion and marked inflammatory reaction of the meninges, which were infiltrated by many polymorphonuclear neutrophils, small round cells, and fungous cells. The cortical tissue was invaded by well-circumscribed areas in which the parenchyma was destroyed, leaving spaces containing only fine fibrillary strands of tissue in which fungous cells were seen (Fig. 5).

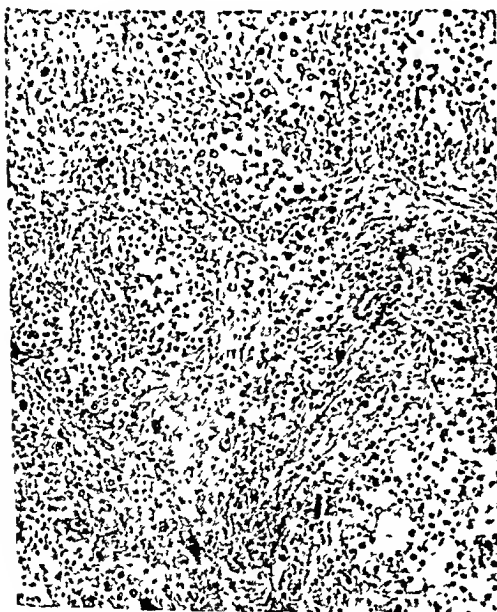


Fig. 4.

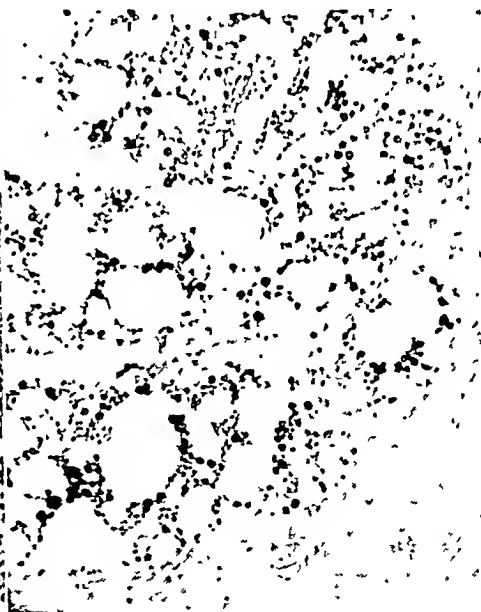


Fig. 5

Fig. 4.—Photomicrograph of a section of the patient's lung. The alveoli are filled with many of the *Cryptococcus* forms as well as inflammatory cells. The alveolar walls are thickened and contain fibrous tissue strands.

Fig. 5.—Photomicrograph of a section of the cortical tissue of the patient's brain. The lesion completely destroys the brain parenchyma and the space is filled with fibrillary strands and *Cryptococcus* forms.

MYCOLOGY STUDIES

On the patient's admission to the hospital scrapings taken from the face, scalp, fingernails, and toenails were examined microscopically in potassium hydroxide. *Candida* was noted in all specimens. The sputum and scrapings

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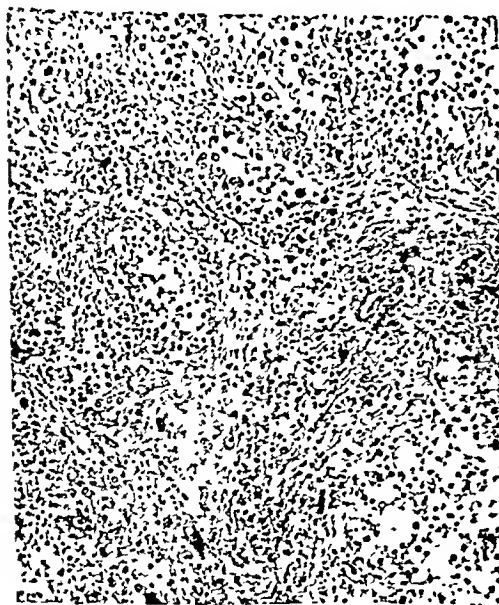


FIG 4

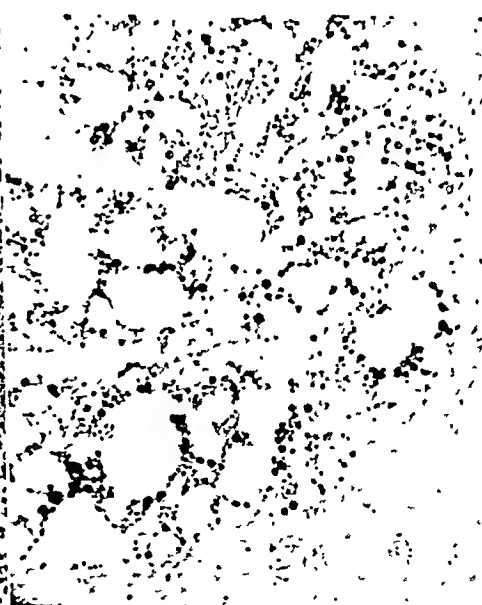


FIG. 5

Fig. 4.—Photomicrograph of a section of the patient's lung. The alveoli are filled with many of the *Cryptococcus* forms as well as inflammatory cells. The alveolar walls are thickened and contain fibrous tissue strands.

Fig. 5.—Photomicrograph of a section of the cortical tissue of the patient's brain. The lesion completely destroys the brain parenchyma and the space is filled with fibrillary strands and *Cryptococcus* forms.

MYCOLOGY STUDIES

On the patient's admission to the hospital scrapings taken from the face, scalp, fingernails, and toenails were examined microscopically in potassium hydroxide. *Candida* was noted in all specimens. The sputum and scrapings



Fig 6

Fig 7

Fig 6—Photomicrograph showing a nest of *Candida albicans* organisms in the cutaneous layers of the skin. This is from a section of a biopsy taken from the toe of the patient.

Fig 7—Photomicrograph showing the elongated monilial fungi in a lesion of the endocardium from a rabbit injected intravenously with a culture of *Candida albicans* from the patient. The culture was from the fingernails.

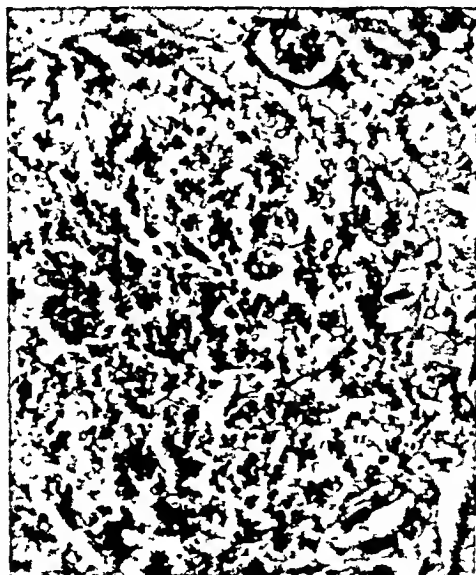


Fig 8—Photomicrograph showing the monilial forms in the renal tissue of the same rabbit as demonstrated in Fig 7.

from the tongue revealed similar fungous cells. India ink mounts were also made of these specimens but no yeasts with capsules were seen. Cultures were taken from the areas listed above and these were subcultured to obtain pure colonies for classification and preparation of an autogenous antigen. A biopsy taken from a toe revealed *Candida* forms (Fig. 6). The mycologic studies were later repeated by the Department of Bacteriology, School of Medicine, University of Southern California. On the basis of culture, carbohydrate reactions and rabbit inoculation, both laboratories concluded that the fungus was *Candida albicans* (Figs. 7 and 8). At this time the study of the cultures appeared to be so conclusive that no additional cultures were made and attention was focussed on the treatment and clinical course. It was not until three months after the establishment of *Candida albicans* as the infecting organism, when meningitic symptoms developed, that additional cultures were taken. These cultures yielded both *Candida albicans* and *Cryptococcus neoformans*. Two hours after death cultures were taken from the blood, brain, lungs, liver, spleen, kidneys, and nails. As shown in Table I, *Candida albicans* was again recovered from the nails, spinal fluid, and urine; *Cryptococcus neoformans* was recovered from these three sites and was the only organism recovered from the brain tissue. Through an accident in the laboratory the cultures from the kidney, lung, spleen, and liver were lost.

TABLE I. ANTE-MORTEM AND POST-MORTEM MYCOLOGY STUDIES

ANTE-MORTEM MYCOLOGY STUDIES			
MATERIAL STUDIED	CULTURES		SECTIONS
	CANDIDA	CRYPTOCOCCUS	
Sputum	+		Candida +
Nails	+		
Skin	+		
Scalp	+		
Tongue	+		
<i>Cultures 48 hours before death</i>			
Urine	+	+	
Spinal fluid	+	+	
POST-MORTEM MYCOLOGY STUDIES			
MATERIAL STUDIED	CULTURES		SECTIONS
	CANDIDA	CRYPTOCOCCUS	
Urine	+	+	
Spinal fluid	+	+	
Brain		+	
Kidney			Cryptococcus +
Lung			Cryptococcus +
Spleen			Cryptococcus +
Liver			Cryptococcus +
Nails	+	+	Cryptococcus +
Pancreas			Cryptococcus +
Adrenals			Cryptococcus +

DISCUSSION

The patient here presented was first observed as a case of generalized cutaneous moniliasis with roentgenographic findings indicating a possible pulmonary infection. The clinical observations were confirmed by laboratory investigation, and therapy was instituted with this diagnosis in mind. The iodide therapy failed; the patient grew progressively worse, and meningitis developed.

The finding of *Cryptococcus* as well as *Candida* in the spinal fluid and urine cultures, both ante mortem and post mortem, together with the occurrence of overwhelming *Cryptococcus* involvement of the tissue of the brain, kidney, lung, spleen, liver, pancreas, and adrenals, brings to attention the fact that occasionally two fungous infections may exist simultaneously in the same individual. This case illustrates clearly the value of repeated frequent cultures. One must constantly be on the lookout for secondary fungi, and only by serial cultures can the time of the secondary invasion be determined. In this case the laboratory findings indicated that the primary pulmonary infection was *Candida* and that the *Cryptococcus* was superimposed terminally. The latter, however, appeared to be responsible for the death of the patient. Another assumption is that a dormant strain of *Cryptococcus* was present from the first along with the *Candida* and that it developed rapidly when the patient's resistance was depleted. On the other hand, since *Cryptococcus* is at times known to occur as a primary pulmonary infection before secondary invasion of the central nervous system, it is possible that the pulmonary lesion in this case was a chronic *Cryptococcus* infection which was not cultured because it was not possible to procure a bronchoscopic sputum specimen, and that the *Candida* recovered from the sputum was in the role of a saprophyte.

During the last few years the literature shows an increasing number of reports of pulmonary and systemic fungous diseases, probably because of improved diagnostic methods for recognizing these diseases. It is important that interest in this group of infections be aroused, since the pulmonary manifestations simulate the more common diseases of the lungs, and early differentiation may save the life of the patient.³⁻⁵

We consider the case reported here unique not only because it occurred in the first decade of life²⁰ but because of the overwhelming secondary *Cryptococcus* infection occurring terminally, superimposed on a rather long-standing *Candida* infection.

SUMMARY

1. A case is presented of an initial chronic infection of *Candida albicans* which occurred in the first decade of life and in which an overwhelming infection by *Cryptococcus neoformans* appeared terminally.

2. The first invading organism found was *Candida albicans*. The organism was identified by clinical manifestations, by culture of morphology, by growth on differentiating carbohydrate media, and by rabbit inoculation.

3. The second organism, found only terminally, was *Cryptococcus neoformans*. Identification was obtained through clinical manifestations, cultural morphology, and carbohydrate media differentiation and animal inoculation.

The photographs are from the Department of Photography, School of Medicine, University of Southern California, at the Los Angeles County General Hospital.

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CONGENITAL DUODENAL ATRESIA

REPORT OF A SUCCESSFUL SURGICAL CASE

CHARLES H. LEECH, M.D., AND ALFRED W. PINKERTON, M.D.

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THE term *atresia* signifies complete occlusion; the infant with congenital atresia of the duodenum lives but a few days unless it receives prompt surgical treatment.

This condition, recognized by Calder as early as 1733, was invariably fatal until 1916, when Ernst recorded the first successful treatment. Miller,³ in 1939, and Ward and Cooper,⁵ in 1943, each reviewed the literature, carefully tabulated the successful cases, and added successes of his own. Later Kautz and co-workers² surveyed the literature concerning congenital duodenal obstructions in general from the viewpoint of the roentgenologist. In 1945 Sumner and Morris⁴ described the case of a patient whom they had treated successfully and whom they believed to be the sixteenth reported survivor.

During the thirty-two years since Ernst's case was published the surgical techniques of dealing with these infants have been greatly improved, largely through the efforts of Ladd, Donovan, Miller, and a few others. Yet today medical literature records the six-month survival of fewer than thirty such patients.

It is difficult to gauge the incidence of this anomaly, but the condition is probably much more common than is generally realized. From figures presented by Davis and Poynter¹ a quarter of a century ago, we may deduce that congenital atresia of the duodenum occurs once in approximately 58,500 live births, and Kautz and co-workers² recently asserted that only about 300 cases have been recorded.

The most obvious symptom is persistent vomiting, usually beginning with the first feeding. Dehydration is rapid, and death commonly occurs during the first week; there is no record of survival beyond the twelfth day without surgical intervention. Exact diagnosis depends upon roentgenologic study of the intestinal tract: absence of gas in the lower intestinal tract indicates atresia, and failure of barium to pass through the duodenum after six hours definitely localizes the occlusion. Such study should be instituted promptly whenever clinical observation or history suggests the possibility of atresia. Alertness to that which is too often dismissed as a trivial symptom and promptness in determining its cause offer the only hope of life to these little patients.

CASE REPORT

A white female infant was brought to us at the age of 10 days with the complaint of having vomited after each feeding since birth.

History.—The patient's birth weight was 6 pounds, 8 ounces. She had been treated by the administration of subcutaneous fluids. To the best of the parents' knowledge no yellow stools had as yet been passed. The family history was non-contributory; one brother and two sisters were living and well.

Examination.—The patient weighed 4 pounds, 15 ounces, representing a weight loss of more than 1½ pounds since birth. A moderate degree of jaundice existed. Upon rectal examination a small amount of bile-stained meconium was obtained; no cornified epithelial cells were found in this meconium. The abdomen was not distended and no pyloric tumor was palpable. The infant was

immediately subjected to roentgenologic study. Plain films revealed an absence of gas in the lower intestine; therefore, barium was administered orally and roentgenograms were made at one, four and one-half, and sixteen hours. The duodenal cap filled easily and showed distention, but no barium left the first portion of the duodenum in sixteen hours.

Treatment.—Preoperative care consisted chiefly of the administration of physiologic saline solution by the subcutaneous route and Synkamin intramuscularly. Gastric lavage preceded surgery.

Through an incision extending from the ensiform to the umbilicus the presence of duodenal atresia was confirmed. After determining that there were no other anomalies present in the intestinal tract, an isoperistaltic posterior gastroenterostomy was accomplished, under open cone ether anesthesia, twenty-four hours after we first saw the patient.



A.



B.

Fig. 1A —Preoperative barium study one hour after oral administration of barium, showing filling and distention of duodenal cap.

Fig. 1B —Preoperative barium study sixteen hours after oral administration of barium, showing complete failure of the contrast medium to pass beyond the duodenum.

Immediately after the operation hypodermoclysis of physiologic saline solution was begun. Boiled water was offered at three-hour intervals and approximately one-half of it was retained. The infant was put on a low-fat formula nineteen hours postoperatively. Early on the second postoperative day parenteral administration of glucose in saline was begun and repeated twice daily until the fifth day, when the patient was put on a regular formula and the daily administration of Zymadrop begun. On the tenth postoperative day ascorbic acid and Drisdol were added to the diet. Pabulum was begun ten days later.

Results.—There was a slight but constant gain in weight from the beginning of treatment onward. When discharged, twenty-six days after operation, the infant weighed 6 pounds, 15½ ounces, and was accepting 4 ounces of formula at normal intervals.

At 3 months of age the child was started on beef and liver soup, potato, strained vegetables, jello, and similar foods.



A.



B.

Fig. 2A —Postoperative barium study of same infant six months later, thirty minutes after oral administration of barium

Fig. 2B —Ninety minutes after oral administration of barium, demonstrating functioning anastomosis and normal passage of the contrast medium

When the patient was 6 months old another barium study was made. X-rays taken at intervals of thirty minutes, one hour, ninety minutes, two hours, and three hours showed the stomach to be emptying satisfactorily. There had been no vomiting since discharge from the hospital. Weight was 14½ pounds, length 25½ inches, head 16¼ inches, and chest 15½ inches at that time. She was then put on a three-meal regime, and her progress continued to be entirely satisfactory when last seen, at the age of 9 months.

SUMMARY

Congenital duodenal atresia is an urgent surgical condition of the newborn. Fewer than thirty six-month survivals have been recorded to date. Appearance of the most obvious symptom, persistent vomiting after feeding, justifies immediate roentgenologic study.

We have reported the case of an infant first seen by us at the age of 10 days and successfully treated by posterior gastroenterostomy.

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NEONATAL ASPHYXIA DUE TO BRANCHIAL CLEFT CYST

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NEONATAL cyanosis and respiratory embarrassment are associated most commonly with such conditions as difficult or instrumental labor, use of prenatal analgesics or anesthetics in the mother, atelektasis, aspiration of amniotic fluid, cerebral birth injury, and prematurity. Yet occasionally tumors and cysts, often in obscure locations, may obstruct the airways and thereby lead to asphyxia and/or death.^{1, 2} Therefore, it is important to search for possible obstructive masses in infants exhibiting neonatal respiratory distress. We wish to present a case of an infant with neonatal asphyxia due to a branchial cleft cyst.

CASE REPORT

C. R., a 7-day-old female infant, was admitted to Freedmen's Hospital May 12, 1947, because of respiratory difficulty present since birth. The family history was noncontributory and the prenatal period was essentially uneventful. Birth occurred May 4, 1947, at another hospital after a full-term gestation. Labor was uncomplicated and lasted four hours. The infant breathed spontaneously at birth and weighed 5½ pounds. Between May 4 and May 8 the infant developed respiratory difficulty. There was inspiratory retraction of the lower end of the sternum. Intermittent cyanosis of the lips, palms, and soles was observed, particularly after feeding. Respirations were noisy and crowing in character and on the day of admission they became rapid. The infant salivated constantly. She appeared to swallow with difficulty and regurgitated frequently during and after feeding. The vomiting was not forceful and vomitus consisted of curdled milk and mucus. The appetite remained good and the infant had a strong sucking reflex. Stools were normal. There were no convulsions.

Physical examination disclosed a poorly nourished, dehydrated, Negro female infant, weighing 5 pounds, 4 ounces. She was active and vigorous. The skin was dry and peeling over the feet, trunk, and arms. The palms and soles were pink. The head, scalp, fontanelles, and ears were negative. The nose, mouth, and pharynx contained a large amount of thick, tenacious mucus. Digital examination of the base of the tongue revealed no palpable tumor masses. The cry was staccato and hoarse. Inspiration was accompanied by marked retraction of the lower end of the sternum and a hoarse stridor. These findings were reduced on sleeping and quiet breathing. The infant appeared more comfortable in the prone position; breathing was easier, less labored, and less noisy. The examination of the heart, lungs, and abdomen was essentially negative.

Under fluoroscopy a soft rubber catheter passed without obstruction through the esophagus into the stomach. An admission roentgenogram of the chest revealed clear lungs, a normal cardiac silhouette, and no mediastinal widening. The admitting diagnosis was laryngeal obstruction of unknown etiology.

The hemogram showed 12,750 white cells and 5.5 million red cells per cubic mm. The hemoglobin was 14.5 Gm. per cent. The blood Kahn was negative.

From the Division of Pediatrics and the Department of Pathology, Howard University School of Medicine and Freedmen's Hospital.

Immediate treatment included oxygen, prone position, intermittent steam inhalations, parenteral fluids, supplementary vitamins, and frequent small feedings. These measures were continued throughout the hospital course.

On May 13 the infant was examined by the consulting otolaryngologist who found nothing of significance. He suggested irradiation of the thymus gland and direct laryngoscopy if no improvement ensued. By May 16 the infant's condition was thought to be improved. Secretions from the nose and throat had diminished and respirations were quieter. However, she continued to exhibit episodes of stridor and costal retraction alternating with periods of quiet normal breathing. Additional therapeutic measures instituted at this time included penicillin, ephedrine sulfate nose drops, and feeding by gavage. Since only periodic improvement in the patient's condition had been noted, on May 22 direct laryngoscopy was done. Direct vision of the epiglottis, larynx, vocal cords, and arytenoids showed no abnormality.

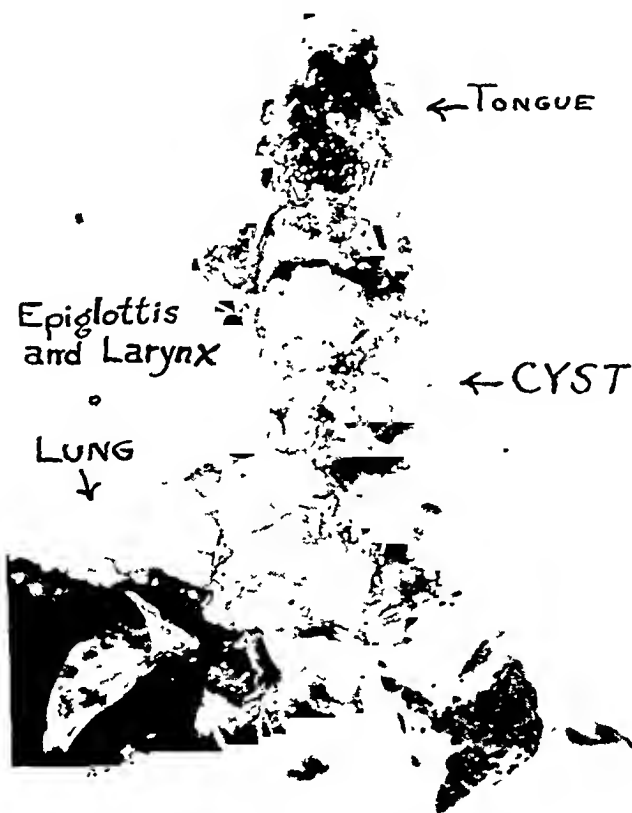


Fig. 1.—Photograph of gross pathologic specimen removed at autopsy demonstrating the cyst in intimate relationship with laryngeal and pharyngeal structures.

The clinical picture continued as before with periodic attacks of stridor and retraction of the thoracic cage alternating with intervals of quiet breathing. The infant was afebrile during the entire hospital course. Repeat roentgenograms of the chest on May 21 and May 27 were negative. The infant expired May 27.

Post-mortem examination of the infant immediately after death revealed a cystic mass in the anterior triangle of the neck on the left side. It was moderately firm, movable, and clearly transilluminated. The inner wall of the mass bulged into the oropharynx as a soft cystic swelling capable of obstructing both larynx and esophagus. Dissection of the neck and thorax exposed a cyst which was situated just posterior and lateral to the upper end of the esophagus. The cyst was soft, thin-walled, and measured 4 by 1.3 by 2.5 cm. The medial wall of the mass was in intimate contact with and covered the cricothyroid muscle and the left anterolateral surface of the larynx. The cyst extended posteriorly and caudally to compress the pharynx, esophagus, and trachea. The left lateral lobe of the thyroid gland was compressed by the cystic structure whose contents consisted of soft cheesy material (see Fig. 1). There were no significant gross findings in the other visceral organs.



Fig. 2.—Photomicrograph of section made through the cyst wall showing stratified squamous epithelium lining, connective tissue stroma, and adjacent thyroid tissue adherent to the cyst wall.

Microscopic Examination.—The cyst was lined by stratified squamous epithelium (see Fig. 2). Sections of the liver showed fatty metamorphosis, immature red blood cells in the sinusoids, and phagocytosed pigment in macrophages. The lungs exhibited patchy emphysema, alveolar and interstitial hemorrhages, edema, and scattered atelectasis. The kidneys showed cloudy swelling and hemorrhages into Bowman's capsule. Sections of the adrenal glands revealed medullary hemorrhages. The pathologic diagnosis was asphyxia caused by a left branchial cleft cyst which compressed the larynx, trachea, pharynx, esophagus, and left lobe of the thyroid gland.

DISCUSSION

Branchial cleft cysts and fistulas often do not manifest themselves in early childhood.^{3,4} Most reports in the literature concern cases in adults and children past infancy.⁴⁻⁷ Baumbartner³ in 1933 reviewed the records of the Chil-

dren's Hospital of Los Angeles and found only four cases of branchial cleft cysts and fistulae, only one of which was apparent at birth. Hyndman and Light,⁸ in reviewing ninety cases, noted that the average age of onset was 17 years. The condition was noticed at birth in 21 per cent of the cases and in only 11 instances was the cyst diagnosed before 11 years of age.

The usual symptoms produced are the presence of a uniform, painless, semifixed, fluctuant, cystic tumor in the neck, and a persistent discharge in the case of fistula. If infection takes place, the symptoms of inflammation, acute or chronic, develop. Occasionally, pain due to local pressure may be present. In the absence of infection such cysts and fistulas usually produce no great discomfort.^{3, 8}

Less commonly, unusual symptoms may be produced. Thomson⁹ reported a case in an adult associated with local pain, husky voice, fixation of the vocal cord, and dyspnea. At operation the cyst was found attached to the left lamella of the larynx and greater cornu of the hyoid and passed inward to the lateral wall of the pharynx. Removal of the cyst relieved all symptoms.

Carp¹⁰ presented a case of a fistula accompanied by an unproductive cough of two years' duration. The fistulous tract was found attached to the vagus nerve. Extirpation of the fistulous tract led to relief of the cough. Similar symptoms of vagal stimulation such as nervousness, restlessness, hoarseness, palpitation, vomiting, pallor, and intermittent pulse may follow probing, pinching, or distention of the fistulous tract.

Smith¹¹ described a fistula in a 3-week-old child whose respiration and deglutition were markedly impaired.

In our case the inner wall of the cyst at times prolapsed over the upper aperture of the larynx and compressed the trachea and esophagus, leading to stridor, obstruction to deglutition and respiration, and eventually to death from asphyxia.

SUMMARY

A case of neonatal asphyxia due to a branchial cleft cyst is presented along with a review of the usual and unusual symptoms accompanying such cyst.

The authors wish to acknowledge the assistance of Dr. John F. G. Clark in the preparation of the pathology report.

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Clinical Conference

CONFERENCE AT THE UNIVERSITY OF ARKANSAS HOSPITAL

WILLIAM A. REILLY, PROFESSOR AND HEAD OF PEDIATRICS

Case 1. Tuberculous Caseous Pneumonia

DR. HAROLD MILLER (Assistant Resident in Pediatrics).—J. L., an 8-month-old white girl, was admitted March 5, 1948, with a history of seeming well until two months before admission, when she developed fever, cough, vomiting, and some respiratory difficulty. There was anorexia and irritability associated with a weight loss of about 3 pounds. The infant's grandfather had died of tuberculosis one year previously and she had been exposed frequently for the past six months to an aunt who had active tuberculosis which was discovered three months prior to admission.

The patient appeared quite ill; rectal temperature was 102.4° F.; the skin of the abdomen was loose; the chest revealed marked dullness on percussion over the entire left lung, sibilant and crepitant râles over both lung fields, and bronchial and amphoric breathing in the left axilla; a firm spleen was palpable about one inch below the costal margin.

The Mantoux test with 0.1 mg. of old tuberculin was positive with a 2.5 cm. area of induration and erythema. Spinal fluid findings were normal, including culture for tubercle bacilli. A chest film (Fig. 1) revealed a multiloculated cavity involving the midportion of the left lung and extending into the hilus, with a diffuse infiltration surrounding the cavity and a widening of the superior mediastinum; the right lung field was clear. Gastric washings showed the presence of acid-fast bacilli.

Streptomycin was administered intramuscularly from March 13 to May 19, 1948, in a dose of 320 mg. daily (25 mg. per pound of body weight) divided into four parts and given every six hours. A total of 21 Gm. was thus administered.

The temperature began to fall from 103° F. daily after the first week of treatment to about 100.6° F. maximum daily, and after the third week remained normal; weight began to increase after the fourth week.

Chest films after three weeks of therapy showed the right lung to be clear with the left lung showing considerable regression in the size of the cavity and the area of involvement, but widening of the superior mediastinum was still present. A film taken forty days after starting streptomycin showed still further diminution in the size of the cavity and also in the width of the superior mediastinum.

Treatment was to be continued at home after May 19, 1948, but was not given. She entered a sanatorium on June 21, 1948. In the next two months she progressed favorably, gained 2½ pounds, remained afebrile, and by the end of September seemed to be quite well. At this time the chest film showed no evidence of residual involvement as compared to a chest film taken on June 21.

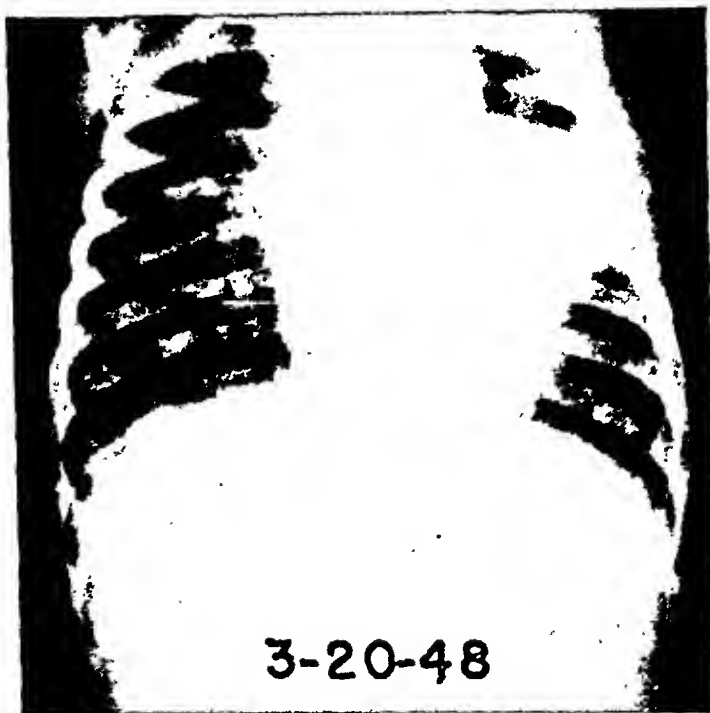


Fig. 1.—Case 1. Tuberculous caseous pneumonia with cavity.



Fig 2.—Case 1. Cavity had diminished considerably three weeks after starting streptomycin. This picture taken three months later did not show a cavity but only slight residual involvement of the left lung. After another three months the lungs were normal roentgenologically.

1948 (Fig. 2) which showed regression of the left superior mediastinal lymph nodes and of the area of involvement adjoining the left hilus. A cavity could no longer be identified.

DR. WILLIAM P. BARRON (Assistant Resident in Pediatrics).—Did streptomycin arrest the disease process?

DR. REILLY.—At this age a spontaneous recovery from this type of tuberculosis is rare. The disease usually terminates fatally. In this case, clinical improvement was apparent shortly after therapy was begun. No dissemination occurred. We feel that streptomycin was responsible for the retrogression of the tuberculous process.

DR. VIDA GORDON (Associate Professor of Pediatrics).—Was the duration of treatment sufficient?

DR. REILLY.—In view of knowledge at that time, it would have been advisable to continue therapy for another three to four months. There are several others who have successfully treated this caseous type.^{1, 2} Unknown to us, therapy was not continued at home as previously arranged.

A brief survey of our results (Table I) with various types of tuberculosis shows that streptomycin has been helpful in four of the seven cases. We have treated others but started too late. P. A. had a tuberculous meningitis which, during three months of therapy, had not progressed clinically. The child has been free of fever, somnolence, weight loss, anorexia, and the other usual evidences of toxicity; frequently she sits and plays; however, there is tremor of the extremities, possibly due to the medication as well as the disease; nuchal

TABLE I. TUBERCULOSIS TREATED WITH STREPTOMYCIN

NAME	AGE	TYPE	DURATION OF DISEASE	DURATION OF THERAPY	TOTAL DOSAGE (50-80 MG. PER KG. PER DAY)	RESULT
1. J. L.	8 mo.	Pulmonary with cavitation	2 mo.	2½ mo.	21 Gm. IM.*	Improvement clinically x-ray findings not completely cleared.
2. R. D.	5 mo.	Meningitis pulmonary with possible cavitation	8 days	2 mo.	20.6 Gm. IT.† and 0.8 Gm. IM.	No improvement; spastic; died a few days after discharge.
3. C. B.	4 mo.	Meningitis and pulmonary	5 weeks	1 mo.	46.6 Gm. IM. and 1.1 Gm. IT.	No improvement.
4. S. H.	4 yr.	Lymphadenitis	6 mo.	3½ weeks	12 Gm. IM.	Marked improvement.
5. W. W.	4 yr.	Meningitis and pulmonary	4 mo.	5 weeks	30.2 Gm. IM. and 0.85 Gm. IT.	No improvement.
6. J. S.	13 mo.	Meningitis and pulmonary	3 weeks	2½ mo.	179.4 Gm. IM. and 0.73 Gm. IT.	Improved
			6 mo.	5 weeks	43.1 Gm. IM. and 0.435 Gm. IT.	No improvement; spastic.
7. P. A.	16 mo.	Meningitis and possible pulmonary	2 weeks	2 mo.	23.6 Gm. IM. and 1.750 Gm. IT.	Improved; still receiving therapy.

*IM. = Intramuscular.

†IT. = Intrathecaly.

rigidity is ever-present; the spleen is palpable, and there has been possible pulmonary involvement. The toxicity, the draining abscess, and biopsy incision in S. H. receded and healed very favorably—much more quickly than during a regime used for six months before streptomycin. The patient may have developed some immunity before streptomycin was started; the antibiotic may have stopped the growth of the tubercle bacilli and thus further aided the patient. J. S. showed improvement after the first course of therapy, but after two months without therapy there was still some evidence of meningitis and spasticity had developed. A second course of five weeks of therapy was given with no improvement and death occurred eight days later.

The other three patients have not responded to this therapy, usually because of the previous duration and dissemination of the tuberculosis.

Case 2. Pertussis Pneumonia

DR. ALICE GAMBLE (Instructor of Pediatrics).—L. M., a 2-month-old Negro female infant, was admitted March 11, 1948, with the chief complaint of continuous paroxysmal coughing. Aside from a mild cold, the baby had been well until six days before admission, at which time a mild temperature elevation, rhinitis, and respiratory difficulty were noticed. Three days before admission the paroxysms of coughing became more frequent and productive of white phlegm. Cyanosis was present during the paroxysms.

On admission the child was acutely ill with paroxysms of coughing every few minutes associated with cyanosis. The respiratory rate was rapid and grunting in character. The weight was 3.3 kg.; pulse, 148; temperature, 99.4° F.; and respiration, 96.

Pertinent physical findings included dilatation of the alae nasi and crepitant, vesicular râles over the right lung fields with impaired resonance over this area, which lead to a diagnosis of right bronchopneumonia. The chest film confirmed this diagnosis. Although four cough plates were taken, only the first yielded a *Hemophilus* organism not definitely identified as *Hemophilus pertussis*. The leucocytes ranged in number from 46 to 67 thousand with 79 to 84 per cent lymphocytes.

This child was given 200 mg. of streptomycin daily in doses of 25 mg. every three hours for eight days (approximately 75 mg. per kilogram daily). In addition, sulfadiazine, oxygen, and sedation were used. Although early the child had twelve to fifteen paroxysms daily; on the fifth day on streptomycin only four mild paroxysms were charted. The streptomycin was discontinued on the eighth hospital day and the patient was discharged two weeks after admission. Her outpatient clinic follow-up revealed an uncomplicated convalescence as manifested by weight gain and disappearance of paroxysms.

DR. GORDON.—Streptomycin alone or combined with sulfadiazine is being used effectively in several parts of the country for whooping cough. We have admitted eleven patients with severe pertussis since January, 1948, all of whom received streptomycin in doses of 50 to 75 mg. per kilogram daily. All of these patients (except one who was moribund at admission) were noticeably improved

within a period of two to five days after beginning streptomycin. In some cases the response was most dramatic in that hard paroxysms would cease in eighteen to twenty-four hours after treatment began. In the case reviewed the prognosis would previously have been poor because of the pneumonia complicating pertussis in a 2-month-old infant. Bradford³ and Hegarty⁴ as early as 1945 demonstrated the bacteriostatic and bacteriocidal effect of streptomycin on mice infected with *H. pertussis* and suggested clinical trials. By clinical evaluation we have felt that their recommendation was warranted.

DR. REILLY.—The question of inherited immunity and placental transfer of antibodies in pertussis is illustrated in another case of a newborn infant whose mother was exposed to whooping cough shortly before delivery. At the time of delivery the mother was having paroxysms of coughing even though she had a history of having had whooping cough as a child. Two weeks after delivery the baby began having typical paroxysms of coughing with vomiting, though she had not been in contact with the infected children. She had an admission leucocytosis of 25,750, 60 per cent of which were lymphocytes. Even though a cough plate did not yield *H. pertussis*, we felt this was a case of either pertussis or parapertussis.

Kendrick⁵ has shown that even in mothers who have had pertussis in childhood, the amount of circulating antibody during adulthood is low and the amount transferred to the fetus even lower. By immunization with pertussis vaccine during pregnancy the effective protection in both the mother and child is raised. In mothers who are pregnant during the winter months and who have large families, it would seem that immunization of the mothers during the last trimester of pregnancy would help protect the infants during the first crucial months of life until active immunization could be started at 2 to 3 months of age as suggested by Di Saint Agnese and Sako. Christie and Peterson showed that such young infants generate pertussis antibodies.

Case 3. Cutaneous Anthrax

DR. EUGENE CRAWLEY (Instructor of Pediatrics).—A 15-year-old boy skinned a steer which died of what later was proved to be anthrax by the state veterinarian. There were thirty head of cattle that died from anthrax in this area during the months of September and October. On October 12, the patient noticed a small vesicular lesion on this right forearm on the volar surface. By October 13, this lesion had become very dark and there was marked swelling for several inches around the dark center. There was regional adenopathy. That night the patient began to have high fever and felt very ill. The patient was admitted on October 16 with a diagnosis of anthrax by his local physician. Smears and cultures for anthrax and agglutinations for tularemia were negative. The principal findings on admission appeared to be typical of anthrax and there were malignant pustules, malignant edema, and right axillary lymphadenopathy. Temperature was 99.6° F., pulse 120, respiration 20. The patient has a pre-existing and apparently unrelated chronic glomerulonephritis. In

view of the renal pathology which could be complicated by sulfonamide therapy and on the basis of successful eradication of anthrax in animals by streptomycin, it was decided to treat this patient with streptomycin. Within twenty-four hours following the initial dose intramuscularly of 500 mg. the patient was improved and 250 mg. were given every three hours for five days until the patient was markedly improved. The edema had almost disappeared and slight fever continued only twelve hours longer. The axillary lymphadenopathy had disappeared on October 22. The patient was discharged on the tenth hospital day with a dry, desquamating area, 3 cm. across, having a small eschar thereon.

DR. REILLY.—This boy acquired anthrax at the same time and in the same area as four adults whom we proved by smear and culture to have cutaneous anthrax. Three of the adults had skinned a diseased cow; the fourth adult's only contact was by dressing her husband's lesions. This is the first known human-to-human acquisition. The adults quickly recovered within two to five days with daily doses for five days of 300,000 to 400,000 units of penicillin and 6 Gm. of sulfadiazine. Smaller doses of penicillin for shorter times (seventy-two hours) have resulted in cures and negative cultures by the second to fifth day (Murphy⁶). Miller⁷ showed that 93 per cent of mice infected with anthrax survived when adequately treated with streptomycin for seven days, 58 per cent survived with penicillin for seven days and 5 per cent with sulfadiazine for seven days. Culturally streptomycin prevents the growth of the anthrax bacillus. Our sensitivity tests with the anthrax cultures from the adults showed that streptomycin was far more effective than penicillin. We felt, but did not prove, that the boy had a septicemia; there was no evidence of a pulmonic form. This is the first record of human anthrax treated with streptomycin.

DR. GAMBLE.—It is possible that the virulence of this anthrax was not great enough to cause a septicemia form in the human, but did so in the cattle. In septicemic cases perhaps it would be best to use all of these antibiotics. Gold⁸ stated that sulfathiazole is the most effective of the sulfonamides.

Case 4. Osteopetrosis

DR. J. A. HARREL, JR. (Assistant Resident in Pediatrics).—D. S., a white boy 15 years, 10 months old, was admitted to the hospital with chief complaint of drainage and pain in both ears, which had been present since he was 6 years of age. Whenever the drainage ceased, the patient would have severe headaches and diminished hearing. The father had noticed some abnormality of the growth of the child's head and mandible for three or four years, but no other abnormality in the skeleton. The child did not attend school because of slow mental development. The patient has never had any fractures.

The family consisted of the father, 38 years old; mother, 44 years old; and five brothers between 5 and 20 years of age. Hereditary diseases, similar complaints, and consanguinity were denied.

The patient was 70 inches tall, his span was 64½ inches, lower (from symphysis to heel) was 36 inches, skull 23½ inches circumference (average is 22½ inches). The nasal bridge was thickened laterally and very shallow. The

mandible was greatly and regularly thickened. The palate was very high and narrow, the orbits were widely separated (ocular hypertelorism), and there was mild exophthalmos present. There was thick, foul-smelling pus filling the left auditory canal and there was a large perforation of the left eardrum. There was also a perforation of the right eardrum with no drainage present. There was normal dental development for the age but marked malposition of teeth and overgrowth of the gingiva. Chest, heart, and abdominal examinations were negative. Genital development was slightly retarded for the age and there was no axillary hair. Skeletal examination revealed uniform thickening of the ulna and radius, clavicles, femora, and the lower one-third of both tibias. Neurological examination was essentially negative except for slight edema of the nasal sides of both optic nerve heads.

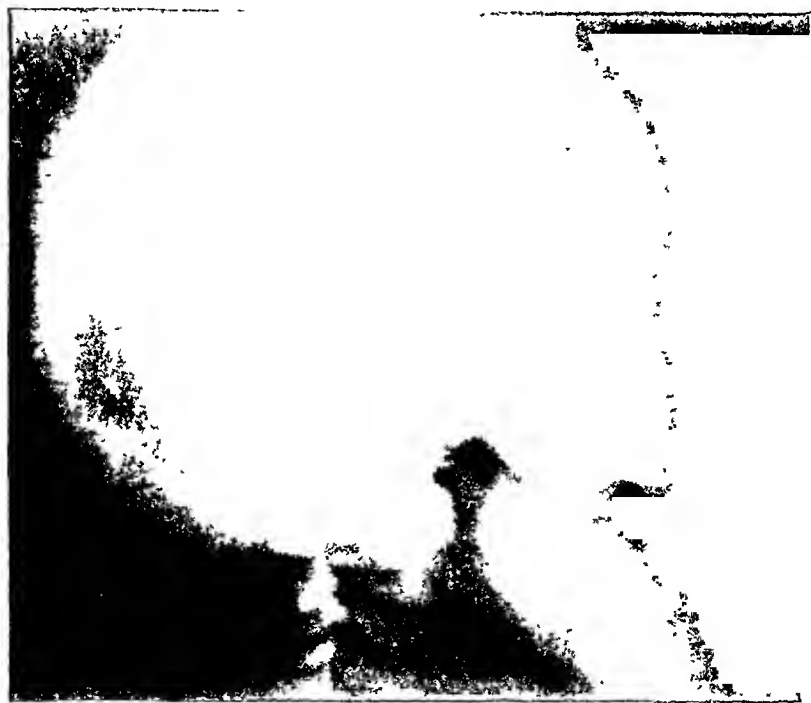


Fig. 3.—Case 4. Osteopetrosis. Note the great thickness and density of all of the skull and facial bones.

Laboratory examinations revealed normal red and white count, adequate hemoglobin and normal differential. The following were the findings in 100 c.c. of blood, with normal values in parenthesis: calcium 11.5 Gm. (9 to 11.5), phosphorus 5.2 mg. (4 to 7.1), alkaline phosphatase 34.5 King-Armstrong units (3 to 13). Serology revealed a negative Kahn. Spinal fluid examination revealed normal findings for the following: pressure, cell count, protein, and sugar. Gum mastie curve and Kolmer test were negative.

DR. I. MESCHIAN (Professor of Radiology).—Routine films of the skull (Fig. 3) and special films of the mandible show a marked sclerosis of all of the bones at the base of the skull and mandible and widening of the diploe of the calvarium, which measures as much as $2\frac{1}{2}$ cm. in thickness. The air spaces of the sinuses are completely obliterated and the clinoids are markedly sclerotic. The bones of the mandible are widened and sclerotic but the teeth appear to be normal. There is no calcium deposit in the pineal gland. The bones are so densely sclerotic throughout the face and skull that all detail is obscured.

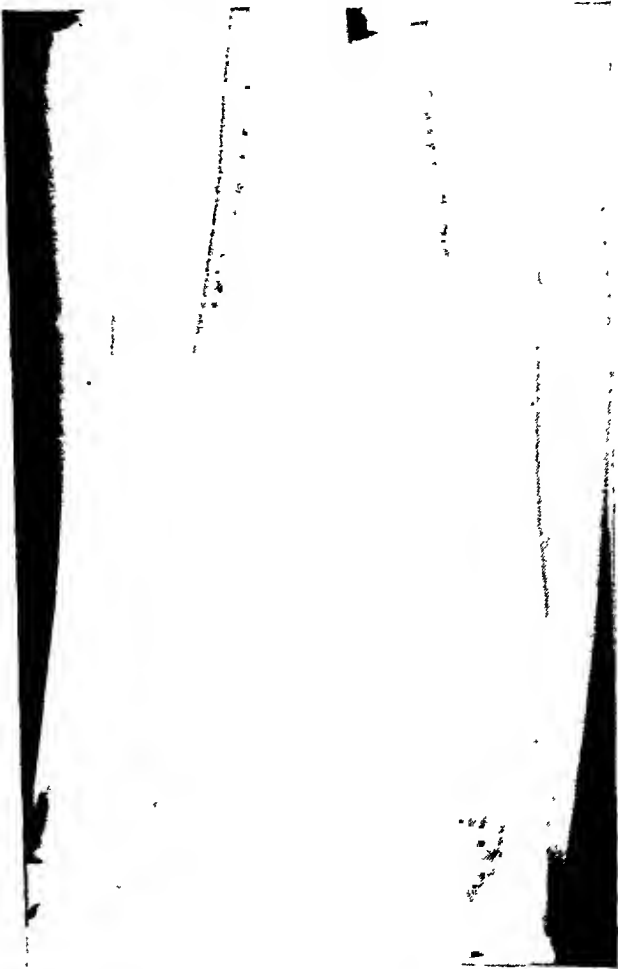


Fig. 4.—Case 4. Osteopetrosis. Diffuse osteosclerosis of cortices and obliteration of medullary cavities.

Anteroposterior films of the ribs and shoulder girdles show a similar marked sclerosis of all the bones of this region. The shaft of the clavicle is widened. Anteroposterior views of the hands, feet, and forearms show a marked sclerosis of the shafts of these bones with considerable endosteal bony proliferation. The long bones are spindle-shaped as a result of this sclerosis, but the carpal and tarsal bones are little involved.

In the legs there is complete obliteration of the medullary portion of the bone by sclerosis with little change in the metaphysis and epiphysis. Antero-posterior and lateral views of the lumbar spine and pelvis show a similar sclerosis of the vertebral bodies and bones of the pelvis. They have a somewhat doubled contour appearance suggesting arrested development at some time in the past. The epiphyses are relatively uninvolved and their age equals the chronological, except for one area which is at the twelve-year age level.

There is diffuse osteosclerosis of all the bones of the body, effecting those of the shoulders, mandible, skull, metaphysis and diaphyses of the long bones predominately. I would consider the most likely diagnosis to be osteopetrosis (Albers-Schönberg disease). Against this is the marked effect on the calvarium proper and the absence of club-shaped long bones. Fluorine poisoning must also be excluded. The vertebrae resemble phosphorus poisoning but the rest of the skeleton does not fit this diagnosis. Paget's disease does not fit the appearance of the long bones and leontiasis ossea likewise cannot be fitted into the appearance below the skull, since this entity is probably a variety of osteitis fibrosa cystica.

MR. LOWELL OZMENT.—Leontiasis ossea and generalized Paget's disease were ruled out; at entry his face strongly suggested acromegaly. He was eunuchoid in proportions and had delayed sexual development.

DR. REILLY.—The chief features of the syndrome are abnormal density of the bones with or without fragility, a strong tendency to anemia which may be severe and fatal, and optic atrophy. There is a distinct familial tendency and the disease is occasionally inherited. It affects all ages and sexes, male individuals slightly more frequently than female. The etiology is unknown. The affliction may be benign or malignant; there may be intermissions, remissions, or complete cessation of the developmental error. As a rule the bones are very hard like marble but soft bones have been reported. Fragility has been exaggerated in the literature. Anemia is usually present, due to the reduction of the blood-forming marrow in the sclerotic bones. The anemia is usually a source of real danger but it by no means corresponds always to the severity of the disease. Serum calcium is usually normal; plasma phosphatase is either normal or slightly low. Optic atrophy may result from thickening about the optic foramina. Nystagmus, hydrocephalus and deafness are other not very uncommon complications. The teeth are prone to decay.

The primary cause of this type of osteoclerosis is a reduction in osteoclastic resorption so that there is a failure in timing of bone apposition and resorption. Investigations of calcium and phosphorus metabolism have led to contradictory conclusions.

Calcium balance studies, further investigation of the high alkaline phosphatase, bone and marrow biopsies were to be done when the family insisted on the boy's help on their farm.

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Psychologic Aspects of Pediatrics

PURE MATERNAL OVERPROTECTION

MATERNAL OVERAFFECTION

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NEW YORK, N. Y.

THE term "overprotection" has been used to characterize the behavior of mothers whose devotion to their children is unusually intense.¹ They allow no competing interest to interfere with their maternal duties and they reduce their other relations in life, marital, social, intellectual, to a minimum.

CLASSIFICATION

Overprotective mothers may be divided into two groups, (1) pure and (2) guilt or compensatory. The "pure" group is made of women who display excessive care for a "wanted" child. The criterion of the "wanted" child is included in order to separate off those mothers who overprotect their children to mask or compensate for a hostility or rejecting attitude of which they are generally unaware.

In addition, there are mixed forms of overprotection and nonmaternal forms. The mixed group includes cases in which an early maternal overprotective attitude disappears later on, most commonly following the birth of a second child. The misbehavior of the older child, stemming directly from the early maternal oversolicitude, may lead to parental rejection. In such instances sibling rivalry is generally a major problem. Shifts in attitude are also seen when a child toward whom the mother had been indifferent suffers a dangerous illness which necessitates much nursing care on her part. In this group may also be included the mothers who, because of business or professional interests outside the home, try to make up for their hours of absence from the child through the intensity of their devotion while with him.

Nonmaternal forms of overprotection, especially by a grandmother living in the patient's home, are frequent. Such cases are often complicated when the young mother is herself not completely emancipated from the daughter relationship and her own marriage is thereby disturbed. The child may also be overprotected by the father, the siblings, the grandfather, other relatives living in the home, a nurse, etc. Marked paternal overprotection is rare, although favoritism, generally for a daughter, is common.

This review is limited to a discussion of pure maternal overprotection or maternal overaffection.

ETIOLOGY

The factors leading to pure maternal overprotection may be divided into three groups: (1) excessive maternal drive, (2) external factors, and (3) emotional privations.

1. *Excessive Maternal Drive.*—The essential feature of pure maternal overprotection is exaggeration of normal maternal behavior. The maternal drive varies in the same way as do all other biologic attributes. When calibrated along a scale of values, it shows a normal distribution curve with a small group of overaffectionate, overprotecting mothers at one end of the curve matched by a similar group of rather indifferent or rejecting mothers at the other end. The overprotecting mother represents a quantitative rather than a qualitative difference in response from the group of mothers as a whole. All the manifestations of the overprotecting mother will be found in a normal sampling of mothers but in milder degree. Similar variations in the intensity of the maternal drive have been observed in lower animal forms.²

That there is a hormonal basis for the maternal drive is indicated by experiments showing that the maternal feeling in animals can be strengthened by injections of pituitary extracts.³ The specific hormone involved is prolactin.³ It is interesting to note in this connection that a high degree of correlation ($r = .579$, $P.E. = .053$) has been established between the duration of the menstrual flow in women and the strength of the maternal drive, women with 6- and 7-day periods showing, on the average, higher scores than those with 2- and 3-day periods, while women with 5-day periods gave an intermediate average score.⁴

There are women who display strongly maternal instincts from early childhood. As children they like to play with and take care of dolls at an age when most girls lose interest in them. They seek out opportunities to take care of other people's babies and they fantasy about having large families. Their relations with boys are often "maternal." At the other end of the scale are the women who, as children, lose interest in dolls at an early age; who are not interested in babies and never fantasy about being a mother and having children.

Levy⁵ negates the viewpoint, suggested by some investigators, that an exaggeration of the maternal instinct necessarily implies a neurosis. He believes that an intense maternal drive can be explained on the basis of innate variability, in most instances reinforced by external factors and emotional privations.

2. *External Factors.*—A long period of waiting for a child is a potent factor. Thus overprotection is frequent when the mother marries relatively late in life, when there is a long period of sterility, when there have been several spontaneous miscarriages, or when a child is adopted after a number of years of trying to have a child. A child is likely to be overprotected if the mother knows, for one reason or another, that she is not going to have more children. Death of a previous sibling or a dangerous illness in the patient himself, a physical or mental handicap, are also factors.

The type of illness in the child and the age of its occurrence are important considerations. As might be expected, an illness associated with alarming manifestations such as convulsions or shock is more likely to influence the mother than a more serious but less stormy illness. Illness in a young infant has a much greater and more lasting effect than when it takes place later on.

Sex difficulties between the parents reinforce maternal overprotectiveness. Levy points out that a wife devoted to her husband cannot be exclusively a

mother. On the other hand normal emotions, not finding an outlet in the inter-parental relations, may well be shunted in the direction of maternity. Absence of the father because of death, divorce, etc., acts in the same way as sex maladjustment. In only four out of the twenty cases of pure maternal overprotection studied by Levy did the marital relations appear normal. Lewenberg⁶ found that sexual maladjustment was almost twice as common in overprotecting mothers as in other mothers.

Social life: There is little social life in common between the parents of overprotected children. This is not to be explained entirely on the basis of sexual incompatibility, since it has been found that many husbands and wives have an active social life together in spite of sexual disharmony. In many instances the overprotecting parent attributes the curtailment of social life to the need to be with the child.

3. *Emotional Privations*, especially lack of maternal love in early life, may create a craving for affection, thereby exaggerating the normal maternal drive. In Levy's series, lack of maternal love was a feature of the lives of most of the women.

Sex of the child: Overprotected children are predominantly boys. Nineteen of the twenty children in Levy's series were boys.

PERSONALITY OF THE OVERPROTECTING MOTHER .

Overprotecting mothers are predominantly responsible, stable, and aggressive. As a group they are good managers, thrifty, reliable, competent. Relatives and friends often turn to them for help and advice. They generally give a story of steady employment before marriage. Aggression, in association with maternity, is seen in many animals, especially in fighting off enemies. It serves to protect the young.

Another prominent feature of the overprotecting mother is thwarted ambition. Many give a history of unfulfilled ambitions for education or a career and this, in turn, gives rise to strong ambitions for the education of the child.

THE PATERNAL ATTITUDE

The fathers of overprotected children are, as a group, submissive, stable husbands and providers who play little part in the rearing of the child. Any attempts which they may make to discipline the child are firmly resented by the mother. In none of Levy's twenty cases could the father be characterized as dominating. Discipline is left largely in the hands of the mother and whatever role the father assumes is determined principally by her. This pattern of behavior has been described as characteristic of American fathers in general. In the case of the fathers of overprotected children, however, the submissive role is exaggerated.

Although most fathers readily adjust to the maternal monopoly and maintain an affectionate relationship with the child, some resent their exclusion from participation in parenthood. They withdraw from the picture and refuse to attempt any disciplinary measures. Their attitude toward the child is then one of indifference or impatience. It is interesting to note that in none of Levy's

eases was there overt hostility. An added factor in some cases is the derogatory attitude of the child toward the father, which is fostered by the mother.

MATERNAL BEHAVIOR

Overprotection is evidenced in the behavior of the mother by (1) excessive care of the child, (2) excessive contact, (3) overprotection against the usual hazards of childhood, and (4) variations in the customary attitude toward training in the direction of overindulgence or domination.

Excessive care refers to the continuation of such activities as feeding, dressing, and bathing the child past the usual age. Breast feeding is apt to be unduly prolonged. The effect of this type of behavior is to retard the psychologic maturation of the child or to "infantilize" him. Excessive contact relates to the tendency of the mothers to remain in constant social relationship with their children. In some instances they continue to sleep with them even in their teens. The mothers manifest their overprotective attitude, further, by protecting the child against the ordinary risks of childhood. They limit the child's play with other children lest he hurt himself, learn bad habits, or contract a contagious disease. They accompany the child to school long after children of similar age are allowed to go alone, or they move near the school so that they can watch the child from the moment he leaves home until he enters school.

Training takes the form of one extreme or the other, indulgence or domination. There seems to be no middle position. Indulgent mothers yield to the demands of their children, allowing them to run riot without regard to the usual rules regarding mealtime, sleeping time, possessions, or organization of the household. The dominated children, on the other hand, are obedient, neat, careful, and polite. In the group as a whole, bladder control is established early.

PROBLEMS OF THE OVERPROTECTED

The problems of the children of overprotecting mothers may be classified into two groups, depending on whether the mothers are indulgent or dominating. According to Levy the principal factor determining the attitude of the mother is the personality of the child. His investigations show that submissive and aggressive behavior are manifested early in life and are most likely based on differences in innate endowment.

The children of overprotecting, overindulgent mothers have a difficult time in making social adjustments, the degree of difficulty being proportionate to the intensity of the maternal attitude. The children are, as a group, demanding, selfish, and tyrannical, anticipating constant attention, affection, and service. They respond to denials of their wishes or to the requirements of discipline with impatience and outbursts of temper or assault. When left alone they are restless unless they are immersed in a book. As a group they are gifted in conversation (owing to their constant association with grown-ups rather than children) and they use every device—charm, wheedling, coaxing, and bullying—to get their own way. This aggressive, demanding behavior of the overprotected has, as its primary aim, maintenance of the originally favored position

with the mother. It differs in this respect from the similar behavior of the emotionally deprived who appear to express in their constant demands for attention an insatiable hunger for things which they have missed.

The extent of the child's misbehavior is roughly proportionate to the parental response. The more the parents give in, the greater is the child's tyranny. In some instances it reaches the point where the child is outspokenly critical of his parents and abusive, or even physically cruel. Such can be the result of a home medium rich in love but poor in discipline.

The problems presented by the children of dominating, overprotecting mothers are principally shyness, anxieties, fears, and submissive behavior.

School.—The evidence of emotional instability is much more apparent in familiar than in unfamiliar surroundings. In contrast to their misbehavior at home, children of the indulgent, overprotected group as a rule give little trouble at school. Indeed, some of them are models of good behavior there and their teachers are often surprised to learn that they are difficult at home. When trouble does occur, it follows the pattern of misbehavior at home; impudence, disobedience, attention-seeking.

School performance is generally good in reading, language, dictation, history, and literature, owing to superiority in verbalization (as a result of constant association with adults), the mother's coaching, and restriction of conflicting play interests.⁷ This superiority generally does not relate to mathematics, where reading ability and vocabulary have the least application.

The children usually like school because they are successful there and because they are temporarily, at least, free from maternal domination.

Friends.—Overprotected children have difficulty in making friends. The principal complaint is that they are too bossy and always insist on being the leaders. They are aggressive, cocky, selfish, and boastful. The mothers often interfere with play and friends. As a result of exclusion from the group and inability to be accepted on an equal status, they often seek as playmates younger children or girls. The difficulty in making friends tends to diminish with increasing age. Even young, overprotected children frequently make a good adjustment at summer camp after an initial period of unhappiness.

Outside Interests.—The principal outside interest of overprotected children is reading. As a rule they avoid rough-and-tumble activities and organized games. Hence the development of strength, agility, endurance, and muscle coordination suffer. Even more important, perhaps, is the loss in social relationships.

Undesirable Habits.—These are no more common in overprotected than in normal children. Feeding problems are perhaps more frequent; on the other hand enuresis is less common.

Sex problems are not notably frequent in overprotected children.

PHYSICAL STATUS

As a group, Levy found the overprotected children to be larger and heavier than other children attending the clinic, possibly owing to the excellent physical care which they had received. Only two of the twenty in his series might be

regarded as obese. Errors of refraction were frequent, possibly because of the excessive reading. Tonsillectomy was more frequent than in other groups.

TREATMENT

An effort should be made to give the mother insight into her overprotecting attitude and its effect on the child. The value of releasing the child from her infantilizing influence should be stressed. The father should be urged to take a more active interest in the family life, develop a friendly relationship with the child, and use his authority as a father.

Interests and activities for the mother outside the home should be encouraged and the parents should participate together in social activities such as visits, trips, vacations, etc. The child, if old enough, needs to realize the mechanism of infantile dependency and tyranny and the importance of behavior suitable to his age. The nursery school, play groups, outings with other children, summer camp, boarding school, are used in order to separate the child as much as possible from the mother.

In an appraisal of the therapeutic methods, Levy found that attempts to give the mother and the child insight into their behavior were of the least value. More useful were interviews with the father. The most effective methods were those which aimed at diluting the mother-child relationship through separating mother and child as much as possible and through stimulating maternal interest in social activities outside the home.

PROGNOSIS

The outlook for the future of the overprotected child is good. The end results of loving a child too much, though occasionally disastrous are generally benign. Once a gain toward independent activity is achieved, the child fights against the infantilizing tendencies of the mother. In this effort he is often assisted by the father. Moreover, the mother is generally willing to assist, also, since she finds relief in lessened responsibility for the child.

Even without treatment, the natural process of maturation tends to release the child from the overprotective attitude of the mother. Merely going to school and being away from the mother for several hours a day are beneficial influences. The process of adolescence is an emancipating force. As adulthood is approached and close competition with colleagues in studies and games becomes less intense, a major factor in the difficult adjustment of the overprotected individual tends to disappear. Furthermore, with increasing age facility in conversation tends to make for popularity and these individuals are often the "life of the party."

PROPHYLAXIS

The most effective way of handling maternal overprotection is prophylactically. It can frequently be anticipated when the "external factors" discussed under "etiology" (a long period of waiting for a child, death of a previous child, earlier, serious illness of the patient, adoption) are operative. Where the child has a physical or mental handicap the mother can be expected to be

overprotective. The whining, demanding, self-centered behavior of many handicapped individuals is directly attributable to parental mismanagement. Not infrequently great assistance can be rendered such cases by repeatedly emphasizing the dire effects of overprotection and the added barrier raised thereby against normal adjustment. In many instances the only treatment of value is psychologic. Even in the absence of these contributing factors it is a simple matter for the pediatrician, who sees the mother and child repeatedly, to recognize excessive maternal drive. In such instances appropriate measures should be instituted before the maternal attitude has become fixed.

SUMMARY

1. Pure maternal overprotection or overaffection is a quantitative rather than a qualitative deviation in the maternal drive.

2. It is to be distinguished from "guilt" or "compensatory" overprotection where the maternal overprotectiveness represents an effort to conceal a rejecting attitude of which the mother is generally unconscious.

3. An innately determined strong maternal drive is generally reinforced (1) by external circumstances, such as a long period of anticipation, serious illness of the child, a physical or mental handicap, and (2) by maternal emotional privations in childhood.

4. Mothers manifest their overaffection by excessive care of the child, excessive contact, overprotection against the usual hazards of childhood, and variations in the customary attitude toward training.

5. Behavior of the child depends on whether the mother is indulgent or dominating. If the mother is indulgent the child is demanding, selfish, and tyrannical. If the mother is dominating the child is shy, anxious, fearful, and submissive.

6. The most effective methods of treatment are those which aim at separating mother and child.

7. The outlook for the future adjustment of the overprotected individual is good. Most develop into well-balanced adults.

8. By early recognition of the circumstances which may lead to overprotection it is possible to institute appropriate measures before the maternal attitude has become fixed.

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Comments on Current Literature

VIRUS ENCEPHALITIS

THE importance of arthropod vectors in the epidemiology of virus encephalitis is becoming increasingly apparent. Papers published in the last ten years report field and laboratory studies which indicate clearly that the tick, the mosquito, and the mite may act as vectors for the viruses of encephalitis, and that these arthropods are potentially capable of playing a significant rôle in the natural history of the summer encephalitides. Of particular interest are the arachnid vectors, the tick and mite, which have been shown capable of passing the viruses of St. Louis encephalitis and of western equine encephalomyelitis transovarially to their offspring.

In a recent article in the *Proceedings of the Society for Experimental Biology and Medicine*,¹ Howitt, Dodge, Bishop, and Gorrie report the isolation of the virus of eastern equine encephalomyelitis from chicken mites, *Dermanyssus gallinae*, and from chicken lice, *Eomenacanthus stramineus* and *Menopon pallidum*. The mites were collected from a chicken house near Shelbyville, Tenn. In several areas of central Tennessee, sporadic cases of encephalitis in children had been reported during the summer of 1947. Chicken mites collected in August, 1947, were triturated in a mortar with 3 c.c. of buffered saline containing 30 per cent normal rabbit serum. After centrifugation the supernatant fluid was injected intracerebrally and intraperitoneally into 12-day-old Swiss mice. A filtrable virus was isolated which was identified by appropriate studies as the virus of eastern equine encephalomyelitis. This isolation represents the first instance that the virus of eastern equine encephalitis has been recovered from an arachnid in nature.

The virus of eastern equine encephalomyelitis was isolated also from chicken lice collected on a farm near Alexandria, Tenn. Since the chicken louse, a member of the order Mallophaga has mouth parts adapted not for sucking but for chewing the surface of the skin and feathers, the authors point out that chicken lice have been observed to feed on young feathers from which the dermal papillae bearing blood vessels, have not yet withdrawn, thus making the drawing and ingestion of blood by the chicken louse possible.

Demonstration of type-specific antibody to the eastern strain in a few chickens and in a single cow from this area seems a significant finding.

The isolation of the virus of eastern equine encephalomyelitis particularly from chicken mites is of considerable interest in light of the findings of other workers in this field. During a nonepidemic year, the virus of St. Louis encephalitis was isolated from chicken mites, *Dermanyssus gallinae*, collected in three widely separated chicken houses in St. Louis County.²⁻⁵ Sulkin⁶ isolated the virus of western equine encephalomyelitis from chicken mites, *Dermanyssus gallinae*, in Dallas County, Texas. Reeves, Hammon, and their coworkers⁷ isolated the western equine virus from bird mites, *Liponyssus sylviarum*, collected in Kern County, Calif. More recently this group of investigators has reported the isolation from bird mites of a mixture of the virus of St. Louis encephalitis and western equine encephalomyelitis virus.⁸ Sulkin and Izumi⁹ recovered the western equine virus from the tropical bird mite, *Liponyssus bursa*.

The isolation of the viruses of St. Louis encephalitis, western equine encephalomyelitis, and now, eastern equine encephalomyelitis, from mites collected in nature, suggests strongly that this arachnid vector plays an important rôle

in the natural history of the summer encephalitides. In the case of St. Louis encephalitis,⁴ it has been shown that transovarial passage of the virus is possible, and that colonies of chicken mites found infected in nature or infected experimentally in the laboratory, harbor the virus for at least two years. It has been demonstrated further¹⁰ that viremia occurs in chickens as a result of the bite of infected mites, and that mites or mosquitoes feeding on such chickens during the period of viremia not only acquire virus but are capable of transmitting the virus by bite to other chickens and to mammals. Mosquitoes infected in this manner are capable of transmitting the virus to chickens and to hamsters.

It will be of considerable interest to follow reports concerning possible transovarial transfer of the virus of eastern equine encephalomyelitis in mites. Of interest likewise will be experiments designed to demonstrate whether mosquitoes feeding on chickens having viremia as the result of the bite of infected mites can acquire the virus and subsequently transmit the virus by bite.

Such a concept of epidemiology, involving two blood-sucking vectors, an arachnid capable of transovarial passage, the reservoir in nature, and an insect, probably the mosquito, capable of transmitting the virus to mammals, including man, would serve to explain some of the unique features of the natural history of the summer encephalitides. Since all three viruses, St. Louis encephalitis, western equine encephalomyelitis, and eastern equine encephalomyelitis, have been isolated from mites collected in nature, it seems possible that similar factors may be involved in the epidemiology of these three virus diseases.

RUSSELL J. BLATTNER.

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News and Notes

Dr. Frederic H. Bartlett of New York died October 19 of a heart attack. Although Dr. Bartlett was 76 years old, he had continued in active practice and had been at his office the previous day. He was for many years attending physician at the Babies Hospital and a member of the faculty of the College of Physicians and Surgeons. He was a member of the American Pediatric Society and served as vice-president in 1937.

Dr. London Snedeker of Boston has retired from active practice to become assistant administrator of the Children's Medical Center of Boston.

Vanderbilt University School of Medicine announces that Professor Arvid Wallgren, of Stockholm, Sweden, will be the next Abraham Flexner lecturer. Dr. Wallgren will arrive in the United States about March 1, 1949.

The original announcement of this Lectureship was made in the fall of 1927 when Mr. Bernard Flexner, of New York City, gave fifty thousand dollars to Vanderbilt University for the purpose of establishing the Abraham Flexner Lectureship in the School of Medicine. This Lectureship is awarded every two years to a scientist of outstanding attainment who shall spend as much as two months in residence in association with either a department of a fundamental science or of a clinical branch. Previous lecturers have been:

Dr. Heinrich Poll, Director of the Institute of Anatomy of the University of Hamburg, Germany.

Sir William B. Hardy, Director of the Low Temperature Research Station at Cambridge University, England.

Dr. Francis R. Fraser, Director of the Medical Unit and Professor of Medicine at the St. Bartholomew Hospital and Medical School, London, England.

Dr. Erik Gunnar Nystrom, Professor of Surgery at the University of Uppsala, Sweden.

Dr. Thorvald Madsen, Director of the State Serum Institute of Denmark.

Dr. Albert Szent Gyorgyi, Professor of Medical Chemistry and Director of the Institute for Medical Chemistry in the Royal Hungarian Franz Joseph's University, Szeged, Hungary.

Dr. Donald D. Van Sloke, member of the Rockefeller Institute and Dr. Warfield T. Longcope, Professor of Medicine, Johns Hopkins School of Medicine.

Sir Edward Mellanby, Secretary of the British Research Council and Chairman, International Technical Commission on Nutrition.

Dr. Wallgren has been Associate Professor of Internal Medicine at Uppsala University and Head of Pediatrics at the Royal Caroline Medical Institute since 1942. He is an Honorary Member of the American Academy of Pediatrics; Canadian Association for the Study of Children's Diseases; Argentine Pediatric Society; and German Pediatric Society. He is co-editor of *Acta Paediatrica* and a member of the Editorial Board of *Annales Pediatrici*; *Pediatrica Danubiana*; *Acta Tuberculosa*; *Archiv für Kinderheilkunde*. He is president of the Swedish Association for Children's Welfare; the Swedish Red Cross Committee on Tuberculosis; the National League Against Tuberculosis; the Save the Children Fund; and Councillor to the State Board of Public Health.

He is widely known in Europe and the United States for his pediatric writings which include over two hundred papers in the field of pediatrics and child health.

The Rochester Child Health Institute announces two assistantships of one year each; one beginning the first of January and one the first of July of each year. These services include preventive medicine in pediatrics with the opportunity of studying normal growth and development, care of the newborn, well child care, psychological problems in young children and school examinations. These are equivalent to fellowships in the sense that opportunities for both service and research are given. The stipend of \$1,620 is offered to suitable candidates. The first available fellowship will be Jan. 1, 1950.

Book Reviews

Psychiatry for the Pediatrician. Hale F. Shirley, M.D., New York, 1948, The Commonwealth Fund, 442 pp. Price \$4.50.

This book is an outgrowth of lectures given by Dr. Shirley to medical students at Stanford University. In its expanded form it is addressed to the large professional audience of pediatricians and general practitioners who are interested in better methods of child guidance in their own practices and who need a comprehensive, yet simple, guide in this field. The author has made a particular effort to suit his text to his audience. He avoids theories and unsettled controversies and shelves involved psychiatric terminology in favor of simple English. He makes a liberal use of case histories. The result is a thoroughly readable book.

The various types of psychiatric problems are covered one by one, and there is an adequate index. However, this book is not primarily intended to be a reference book to which the pediatrician will refer when he encounters a given case. The author intends, rather, that it be read through, and hopes that in doing so the reader will gain a point of view along with a practical foundation of knowledge upon which he can build. After a brief but lucid discussion of basic principles of psychiatry and child guidance, there is a section on development and habit training, followed by a detailed consideration of the role in childhood behavior disturbances of: physical factors, intellectual factors, emotional factors, sexual factors, and environmental factors. There is a wealth of practical information in these chapters. Finally, the author concludes with two chapters on the investigation and treatment of behavior problems.

In order to gain perspective for this presentation, Dr. Shirley reviewed the records of the first 1,000 patients seen in the Stanford University pediatric-psychiatric unit. As a result the choice of material has a foundation in practical experience. It represents, however, the practical experience of a psychiatric clinic, which perhaps explains the dearth of space given to the preventive mental hygiene aspects of ordinary practice.

Dr. Shirley does not attempt to define the limitations of the practitioner in handling these problems in children. He believes that a great deal can be accomplished by those who have the interest and who will take the time to learn the fundamentals. His book should be a great help to this group.

BAKWIN

Stethoseopic Heart Records, Columbia Album No. CM-735 (Revised). George D. Geckler, M.D.

The set consists of four, double-faced records, on which are recorded auscultatory cardiac findings. Normal heart sounds are frequently repeated for comparison with abnormal sounds. Practically all types of abnormal cardiac sounds are recorded, especially the arrhythmias. The various types of abnormalities are described by a preceding commentary.

The sounds and descriptions are very clear. These recordings should be of interest to all physicians and particularly to medical students and teachers. They should be especially suited to group teaching.

CARSON

Hearing and Deafness: A Guide for Laymen. Edited by Hallowell Davis, M.D., Director of Research, Central Institute for the Deaf, and Research Professor of Otolaryngology, Washington University School of Medicine, St. Louis, Mo. Illustrated. New York, 1948, Murray Hill Books, Inc., 468 pages. Price \$5.00.

Of the 30,000,000 children of school age in the nation, some 18,000 are totally deaf, and "our best estimate is that from 1,500,000 to 2,000,000 children in the United States have defective hearing." The *raison d'être* for this excellent collection of articles which deal with the problems of the deaf and hard-of-hearing is thus clearly established. For Dr. Davis "audiology" is truly "a meeting of varied specialists." He has brought together, in one volume, physician, speech educator, speech therapist, teacher for the deaf, psychologist, and field worker to explain to the doctor and his patient the problems which confront the acoustically handicapped individual. The fourteen collaborators cover the field in a thorough fashion.

The title of the book is unfortunate, for the pediatrician can profit from a reading of it. The techniques of audiometry, both the pure tone and work-sentence types, are discussed. The importance of an early diagnosis of defective hearing and an early start in speech training and in *speech conservation* is emphasized. "The confusions caused by imperfect hearing often lead to a progressive deterioration of the ability to discriminate (various sounds). . . . In consequence, every acoustically handicapped child who can benefit from a hearing aid should be fitted with his own instrument as soon as he is ready for it." Education should begin at the nursery school level and should be approached from the oral point of view, as the authors definitely feel "that it is possible, practical, and desirable to teach even totally deaf children to speak and to read speech." Despite the severity of the handicap, recent studies at the Central Institute for the Deaf have shown an educational retardation of only two to three years among their pupils. The problems of the older child and the adult with acquired hearing defects which have to do with the choice of a vocation and the attainment of social maturity are freely discussed. Attention is directed toward the important role of the ever-present, but seldom realized, *auditory background* in our daily lives. Methods of speech reading, of auditory and speech training, both for child and adult, are pointed out. More emphasis could have been placed on the usefulness of similar methods of speech training in the treatment of the acoustically normal child whose articulation is faulty.

The volume can be recommended for patient and parent. The chapters on the medical and surgical aspects of deafness are very well written from the layman's point of view; those on hearing aids should be helpful, and the discussions of educational methods, vocational problems, psychology, and organizations for the deaf will be interesting to him. Much of the material, however, particularly that on the physics of sound perception, anatomy of the ear, vacuum tube circuits, and the interpretation of audiograms, may be beyond his reach. In all, the book should be more readily appreciated by the physician and by those who deal with the problems of the deaf.

FORBES.

Handbook of Orthopaedic Surgery, ed. 3. A. R. Shands, Jr., St. Louis, Missouri, 1948. The C. V. Mosby Company. Price \$6.00.

The first edition of this excellent handbook on orthopaedic surgery was particularly designed to present the fundamental facts and principles of orthopaedic surgery to the medical student and the general practitioner. It served this purpose well, and the third edition will continue to do so. The essential points in etiology, pathology, diagnosis, and treatment of all of the conditions embraced by orthopaedic surgery, except fresh fractures, are covered in such a manner as to make the book an excellent source of reference for physicians in every specialty, particularly pediatrics. An outstanding feature of all editions has been the excellent bibliography which is arranged uniquely according to subjects discussed in each chapter. This permits references to be quickly obtained on any subject. The bibliography in this third edition has been brought up to date so that articles published as late as 1947 are included. The book is strongly recommended for the purpose for which it was originally intended.

HAMPTON

Editor's Column

MR. EWING'S REPORT TO THE PRESIDENT

THE unexpected and amazing victory of President Truman on November 2, which swept into power a Congress of his own party, is a mandate of the people for legislation putting into effect the principles and proposals upon which he based his campaign. This is the very essence of democracy and of our political system. One of the important proposals made by the President was extension of social security and better medical care for the American people.

In light of this, our thoughts have turned to the report of Oscar R. Ewing, Federal Security Administrator, which was published last September, entitled "The Nation's Health, a ten year program."

In January of this year the President asked Mr. Ewing "... to undertake a comprehensive study of the possibilities for raising health levels and to report to me, at your early convenience, upon feasible goals which might be realized by the American people in the next decade." As a part of the study, Mr. Ewing called the National Health Assembly which met in Washington last May, and much of the report is based on the findings of the Assembly. On the issue of national health insurance agreement could not be reached, and Mr. Ewing in his report sides with the proponents. This was quite within his rights and in keeping with his previous statement that his report would not be bound by the findings of the Assembly.

We have refrained from commenting on the report previously as it has been claimed that it was a politically inspired document and campaign propaganda. Regardless of all this, in our opinion it is today, in light of the November election, a document of vital importance to the physician, as beyond question it presents the plan in a broad way upon which proposed legislation will be based in the next Congress. We urge every physician to read the report so that he may have a first-hand idea of the medical legislation which will be proposed. It may be obtained from the Superintendent of Documents, U. S. Government Printing Office, Washington, D. C., price \$1.00.

B. S. V.

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